Copy for the Elected Office (EO/US) PCT/SE00/01079

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

BERGVALL EFTRING, Stina, Lena
Dr Ludwig Brann Patentbyrå AB
P.O. Box 17192
S-104 62 Stockholm
SUÈDE

Date of mailing (day/month/year)	
23 October 2001 (23.10.01)	
Applicant's or agent's file reference P04646PC00	**IMPORTANT NOTIFICATION**
International application No. PCT/SE00/01079	**International filing date** (day/month/year) 26 May 2000 (26.05.00)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
ACTIVE BIOTECH AB P.O. Box 724 S-220 07 Lund Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SBL VACCIN AB Lundagatan 2 S-105 21 Stockholm Sweden	SE	SE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Céline Faust
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 004393361

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 20 February 2001 (20.02.01)	
International application No. PCT/SE00/01079	**Applicant's or agent's file reference** P04646PC00
International filing date (day/month/year) 26 May 2000 (26.05.00)	**Priority date** (day/month/year) 28 May 1999 (28.05.99)
Applicant FOLKESSON, Anders et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

20 December 2000 (20.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P04646PC00/HA		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE00/01079	26.05.2000	28.05.1999
International Patent Classification (IPC) or national classification and IPC7		
C 07 K 14/225, A 61 K 39/12		
Applicant		
ACTIVE BIOTECH AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.12.2000	24.09.2001
Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88 Telex 17978 PATOREG-S	Authorized officer Yvonne Siösteen/EÖ Telephone No. 08-782 25 00

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

ational application No.
PCT/SE00/01079

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-3 and 5-13, 67 , as originally filed
pages _____ , filed with the demand
pages 4 , filed with the letter of 05.09.2001

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under article 19
pages _____ , filed with the demand
pages 15 and 16 , filed with the letter of 05.09.2001

☒ the drawings:
pages 1-4 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

☒ the sequence listing part of the description:
pages 14-66 , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item I and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

tional application No.
PCT/SE00/01079

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 10 and 11

because:

☒ the said international application, or the said claims Nos. 10 and 11
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____ .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

tional application No.
PCT/SE00/01079

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-9, 12-13	YES
	Claims		NO
Inventive step (IS)	Claims	1-9, 12-13	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-9, 12-13	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The claimed invention relates to peptides encoded by nucleotide sequences from Salmonella for use in medicine. The sequences encode two fimbrial structures of Salmonella enterica subspecies I and Salmonella enterica subspecies I serovar Typhi. It has been found that SEQ ID NO 1 is specific to all Salmonella enterica subspecies I. The peptides and the nucleotide sequences encoding them are very suitable for use in diagnosis and in vaccine preparations.

It is already known from Folkesson et al., Abstracts of the General Meeting of the American Society for Microbiology 97, page 219 (1997) that the fimbrial genes safA, safB and safC from Salmonella have been identified.
The genes safA, safB and safC are encoded by parts of the nucleotide sequence SEQ ID NO 1 of Sequence listing No.1 of the present application.

The sequences have, however, not been disclosed in the prior art. Neither have the unique specificities of the genes been known before. Because of their specificity they are very useful in vaccine preparations.

Therefore the claims are considered to be novel and to involve an inventive step.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01079

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07K 14/225, A61K 39/112
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07K, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Abstracts of the 97th General Meeting of the American Society for Microbiology, May 4-8,1997, Miami Beach, Florida, A. FOLKESSON et al: D-67. "Cloning and Characterization of Genes Encoding a Novel Salmonella spp. Adhesive Structure". See abstract. ---	1-4,6,8,10, 13-14
P,X	Molecular Microbiology, Volume 33, No 3, 1999, Anders Folkesson et al., "j Multiple insertions of fimbrial operons correlate with the evolution of Salmonella serovars responsible for human disease", page 612 - page 622, see entire document --- --------	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 October 2000	23 -10- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Henrik Nilsson/GH Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE00/01079

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-11
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet *

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

*

Claims 10-11 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

BRANN

To
THE SWEDISH PATENT OFFICE
Stockholm

International patent application no PCT/SE00/01079
Our ref: P04646PC00/HA:sd

With reference to our telephone communication of September 13, 2001, we wish to file the enclosed page 16, comprising amended claim 14.

The amendment consists of a specification of the purpose of the diagnostic method wherein the primers or probes of the invention are used, by adding at the end of the claim the passage "for the purpose of detecting *Salmonella enterica* subspecies I". A basis for this amendment may be found in the description, e.g. on page 7, lines 20-22 and lines 27-29.

Stockholm, September 13, 2001
Active Biotech AB et al
by:

Harriet Allee

DR LUDWIG BRANN PATENTBYRÅ AB. Intellectual Property & Law Firm.
Stockholm Office: Box 171 92, S-104 62 Stockholm, Sweden. Visiting address: Maria Skolgata 83. Tel: +46 (0)8 429 10 00. (Non-Office hours: 429 10 99) Fax: +46 (0)8 429 10 70 (Patents). Fax: +46 (0)8 429 10 80 (Trade Marks). **E-mail:** brann@brann.se
Uppsala Office: Box 1344, S-751 43 Uppsala, Sweden. Visiting address: Drottninggatan 7. Tel: +46 (0)18 56 89 00. Fax: +46 (0)18 56 89 39.
Head Office and Seat of the Board: Stockholm. Reg. No. 556483-6219. Members of the Association of Swedish Patent Attorneys. Authorized representatives before the EPO and the OHIM

9. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2), has been inserted and, optionally, a pharmaceutically acceptable carrier.

10. A method for protection against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to any of claims 4, 6, and 8.

11. A method for protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to any of claims 5, 7, and 9.

12. Antibodies directed against a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

13. Peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

14. Primers for, or probes that hybridize with, a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method for the purpose of detecting *Salmonella enterica* subspecies I.

09/926596
13 Rec'd PCT/PTO 26 NOV 2001

BRANN

To
THE SWEDISH PATENT OFFICE
Stockholm

International patent application no PCT/SE00/01079
Our ref: P04646PC00/HA:sd

With reference to our telephone communication of September 2, 2001, we wish to file the following pages, comprising amendments as specified herein below:

Amendments

In the description:

On page 4, under the heading "Sequence listing", the words " Sequence Listing No.1, herein referred to as" have been inserted before "SEQ ID NO 1", and the words "Sequence Listing No. 2, herein referred to as" have been inserted before "SEQ ID NO 2".

In the claims:

In new claims 1-4, 6, 8 and 12-14 the words "SEQ ID NO 1" have been put in parenthesis and the words "Sequence Listing No.1" have been inserted before the parenthesis.

In new claims 1-3, 5, 7, 9 and 12-14 the words "SEQ ID NO 2" have been put in parenthesis and the words "Sequence Listing No.2" have been inserted before the parenthesis.

Furthermore:

New claim 1
line 1: "protein" has been amended to "peptide";
lines 1-2: "the group consisting of " has been deleted:
line 2: "or parts thereof" has been deleted;

New claim 2
line 1: "the protein" has been amended to "a peptide";
line 2: "the group consisting of " has been deleted;
line 3: "or antigenic fragments thereof" has been deleted;

New claim 3
line 1: "the group consisting of " has been deleted;
line 2: "or parts thereof" has been deleted;

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Head Office and Seat of the Board: Stockholm Reg. No. 556483-6210. Members of the Association of Swedish Patent Attorneys. Authorized representatives before the EPO and the OHIM.

New claim 4
line 2: "the protein" has been amended to "a peptide";
"or parts thereof" has been deleted;
"the nucleotide sequence according to" has been amended to "a nucleotide sequence selected from";
line 4: "the protein encoded by SEQ ID NO 1" has been amended to "said peptide";
"or antigenic fragments thereof" has been deleted;

New claim 5
line 2: "the protein, or parts thereof," has been amended to "a peptide";
line 3: "the nucleotide sequence according to" has been amended to "a nucleotide sequence selected from";
lines 3-4: "the protein encoded by SEQ ID NO 2" has been amended to "said peptide";
"or antigenic fragments thereof" has been deleted;

New claim 6
line 2: "SEQ ID NO 1, or parts thereof" has been amended to "a nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1)";

New claim 7
lines 2-3: "SEQ ID NO 2, or parts thereof" has been amended to "a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2)";

New claim 8
line 3: "SEQ ID NO 1, or parts thereof" has been amended to "a nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1)";

New claim 9
line 3: "SEQ ID NO 2, or parts thereof" has been amended to "a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2)";

New claim 12
line 1: "the protein" has been amended to "a peptide";
line 2: "the group consisting of" has been deleted;
lines 2-3: "or antigenic fragments thereof" has been deleted;

New claim 13
line 1: "Protein" has been amended to "Peptide";
line 1-2: "the group consisting of" has been deleted;
line 2: "or parts thereof" has been deleted;

New claim 14
line 2: "the group consisting of" has been deleted.

Basis for the amendments

The description

The insertion on page 4 in the description is for a clarifying purpose only: it makes clear that by the wording "SEQ ID NO 1" (and 2 respectively) is meant "Sequence Listing No. 1" (and 2 respectively), conforming better to the established terminology within the field.

The claims

New claim 1 refers to the use of a peptide (instead of a protein)

A basis for the use of a peptide may be found e.g. on page 6, first paragraph, where a method of obtaining a peptide according to the invention is outlined, and on page 6, third paragraph, where medical uses of such peptide are mentioned.

Similar amendments (from protein to peptide) to claims 2-5 and 12 and 13 have the same basis in the description.

All other amendments to the claims relate to linguistic improvements.

Stockholm, September 4, 2001
Active Biotech AB et al
by:

Harriet Allee
Harriet Allee

of respective phage insert is represented by horizontal bars. Name and size of the phage inserts are indicated on the left side of the figure.

Figure 2: Schematic representation of the pTY52 cosmid comprising the *tcf*-operon (SEQ ID NO 2).

A *tcf* specific PCR fragment of 11105 bp was cloned into the Expand vector I cosmid (Roche). The insert is represented with a thick black line while vector sequences are represented with thin lines. Relevant restriction sites sequences are indicated. The position of the *tcf*-operon, i.e. *tcfA, B, C* and *D* (SEQ ID NO 2), is represented by a shaded arrow.

Figure 3: The phylogenetic distribution of the identified genes on the cs7 insert was investigated using the well defined SARC collection, see Example 1.

Figure 4: A 2 kb large internal *Eco*R I fragment was used as a probe in a Southern blot of the SARC collection, see Example 2.

Sequence listing

Sequence Listing No. 1, herein referred to as SEQ ID NO 1, —DNA sequence of the genes encoding the precursor of the saf fimbrie unit of *Salmonella enterica* subspecies I.

Sequence Listing No. 2, herein referred to as SEQ ID NO 2, —DNA sequence of the genes which encode the precursor of the tcf fimbrie unit of *Salmonella enterica* subspecies I serovar Typhi.

Deposit information

The phages carrying the inserted SEQ ID NO 1, i.e. phages clones B1, D1, F11 and N10 (see Figure 1) have been given the ECACC Accession numbers 99051922, 99051923, 99051924, and 99051925, respectively.

The cosmide carrying the inserted SEQ ID NO 2, i.e. cosmide pTY52 (see Figure 2) has been given the ECACC Accession number 99051926.

The depositions were made May 19, 1999.

Detailed description of the invention

The present invention is based on the finding that two fimbrial operons, the *saf* operon and the *tcf* operon, are specific for *Salmonella enterica* subspecies 1 bacteria. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as detection methods for *Salmonella enterica* subspecies I. The *saf* operon is specific for all *Salmonella enterica*

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/73336 A1

(51) International Patent Classification[7]: C07K 14/225, A61K 39/112

(21) International Application Number: PCT/SE00/01079

(22) International Filing Date: 26 May 2000 (26.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9901961-4 28 May 1999 (28.05.1999) SE

(71) Applicant (*for all designated States except US*): **ACTIVE BIOTECH AB** [SE/SE]; P.O. Box 724, S-220 07 Lund (SE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **FOLKESSON, Anders** [SE/SE]; Råsundavägen 169B, S-169 36 Solna (SE). **NORMARK, Staffan** [SE/SE]; Valhallavägen 126 2tr, S-114 41 Stockholm (SE). **LÖFDAHL, Sven** [SE/SE]; Adolfsbergsvägen 36, S-168 66 Bromma (SE).

(74) Agents: **BERGVALL EFTRING, Stina, Lena** et al.; Dr Ludwig Brann Patentbyrå AB, P.O. Box 17192, S-104 62 Stockholm (SE).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/73336 A1

(54) Title: FIMBRIAL PROTEINS

(57) Abstract: The present invention is based on the finding that two fimbrial structures are specific for *Salmonella enterica* subspecies 1 bacteria. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as for detection of *Salmonella enterica* subspecies I.

FIMBRIAL PROTEINS

Field of the invention

The present invention is based on the finding that two fimbrial operons, the *saf* operon and the *tcf* operon, are specific for *Salmonella enterica* subspecies 1 bacteria and therefore have therapeutic use. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as for detection of *Salmonella enterica* subspecies I. The *saf* operon is specific for all *Salmonella enterica* subspecies 1 bacteria and the *tcf* operon is specific for the serovar Typhi of *Salmonella enterica* subspecies 1.

All or part of the DNA-sequences of the genes encoding these proteins can be used as active agents in a vaccine against diseases caused by the *Salmonella enterica* subspecies I bacterial strains or for detection of said bacterial strains.

The present invention also relates to methods of isolating these fimbrial proteins, to antibodies directed against these proteins, and to a vaccine composition comprising these proteins or antibodies directed against these proteins for use in the treatment of infections caused by the *Salmonella spp.* The fimbrial proteins according to the invention or antibodies directed against them can be used for detection of *Salmonella spp.* bacteria.

Background of the invention

The members of genus *Salmonella spp* colonize and infect a wide range of different organisms. Many cause gastroenteritis and enteric fever in humans and domesticated animals while others are not associated with human disease (Saylers et al, 1994). The genus has been divided into two species, *Salmonella bongori* and *Salmonella enterica* where *enterica* can be further subdivided into seven subspecies, designated I, II, IIIa, IIIb, IV, VI, and VII (Reeves et al, 1989). *Salmonella enterica* subspecies I are preferentially associated with warm-blooded animals. Over 99% of all clinical *Salmonella* isolates are strains belonging to this subspecies, including serovars Typhimurium and Enteritidis, which are the major causes of *Salmonella* induced gastroenteritis in humans, and Typhi, the human specific causative organism of typhoid fever, the most severe form of human salmonellosis (Popoff et al, 1992).

Salmonella enterica subspecies I consists of over 1300 different serovars and is preferentially associated with warm-blooded animals (Bäumler, 1997). Over 99% of all clinical *Salmonella* isolates are strains belonging to this subspecies,

including serovars Typhimurium and Enteritidis, which are the major causes of *Salmonella* induced gastroenteritis in humans, and Typhi, the human specific causative organism of typhoid fever, the most severe form of human salmonellosis (Popoff and Le Minor, 1992).

Today gastroenteritis and enteric fever can neither be prevented nor treated with good results. Typhoid fever is a substantial public health problem in developing countries. Each year 33 million people become ill and over 500 000 people die from this infection (American Institute of Medicine, 1986). Typhoid fever can be prevented by vaccination with attenuated bacteria, such as Ty21 and Vi vaccines and whole cell vaccines. Whole cell vaccines show a high incidence of side effects (Ashcroft et al, 1964, Yugoslav Typhoid commission, 1964). The vaccines consisting of attenuated strains of Salmonella typhi suffer from serious drawbacks. They must be administered as three or four spaced doses in order to stimulate protective immune responses (Levine et al, 1989). The treatment of Salmonella typhi with antibiotics is jeopardized since there are strains of Salmonella typhi that are resistant to chloramphenicol, ampicillin, and trimethoprim as well as ciprofloxacin (i.e. multidrug-resistant strains) (Rowe et al, 1997).

Accurate detection of *Salmonella enterica* subspecies I is today not possible. *Salmonella enterica* subspecies I can today only be detected by antibodies directed against surface proteins of *Salmonella enterica* subspecies I. The use of the sequences according to the invention makes it for the first time possible to rapidly and accurately determine the presence of *Salmonella enterica* subspecies I.

For many pathogenic bacteria, there is evidence that the filamentous surface protein structures called pili (fimbriae) are connected to the adhesion of the bacteria to the host cells. Pili proteins are very antigenic and are easily purified. Therefore pili preparations have been used as antigens for vaccination.

Summary of the invention

The invention relates to the objects as defined in the claims. The main object of the present invention is to provide two fimbrial proteins that are specific for *Salmonella enterica* subspecies I bacterial strains, the nucleotide sequences

encoding said proteins, as well as the corresponding amino acid sequences of for therapeutic and diagnostic use. Further are recombinant microorganisms provided, in which the nucleotide sequences according to the invention have been inserted.

An object of the present invention is to provide vaccine compositions for use in the treatment of *Salmonella enterica* infective strains, essentially pure Saf and Tcf fili protein of *Salmonella enterica* subspecies I and *Salmonella enterica* subspecies I serovar Typhi, respectively, as well as antibodies directed to these fili proteins.

A further object of the present invention is to provide the DNA sequences of the genes encoding the Saf and Tcf proteins. These sequences can be used for recombinant production of the proteins and for the preparations of vector vaccines against *Salmonella enterica* subspecies 1 and *Salmonella enterica* subspecies 1 serovar Typhi, respectively, as well as for diagnostic purposes.

Yet another object of the present invention to use purified Saf and Tcf protein from *Salmonella enterica* subspecies 1 bacteria for active or passive immunization of mammals, i.e. the proteins according to the invention can be comprised in a vaccine composition or be used to raise antibodies which can be comprised in a vaccine composition.

Finally, an object of the present invention is to provide a method for preventing or reducing the possibility of *Salmonella* infection of a mammal by administering the vaccines according to the invention. The invention may be more fully understood by reference to the following drawings and detailed description.

Brief description of the drawings

Figure 1.

Schematic representation of phage clones (named N10, D1, B1, F11) covering the entire cs7 insert of *Salmonella enterica* serovar Typhimurium strain SR χ 3181, i.e. comprising the *saf* fimbrial operon, i.e. *safA, B, C* and *D* (SEQ ID NO 1).

The clones were selected from partial *Eco* RI and *Bam*HI libraries in the Lambda Dash II vector. The cs7 insert is represented by a bold line. The extent

of respective phage insert is represented by horizontal bars. Name and size of the phage inserts are indicated on the left side of the figure.

Figure 2: Schematic representation of the pTY52 cosmid comprising the *tcf*-operon (SEQ ID NO 2).

A *tcf* specific PCR fragment of 11105 bp was cloned into the Expand vector I cosmid (Roche). The insert is represented with a thick black line while vector sequences are represented with thin lines. Relevant restriction sites sequences are indicated. The position of the *tcf*-operon, i.e. *tcfA, B, C* and *D* (SEQ ID NO 2), is represented by a shaded arrow.

Figure 3: The phylogenetic distribution of the identified genes on the cs7 insert was investigated using the well defined SARC collection, see Example 1.

Figure 4: A 2 kb large internal *Eco*R I fragment was used as a probe in a Southern blot of the SARC collection, see Example 2.

Sequence listing

Sequence Listing No. 1, herein referred to as SEQ ID NO 1, —DNA sequence of the genes encoding the precursor of the saf fimbrie unit of *Salmonella enterica* subspecies I.

Sequence Listing No. 2, herein referred to as SEQ ID NO 2, —DNA sequence of the genes which encode the precursor of the tcf fimbrie unit of *Salmonella enterica* subspecies I serovar Typhi.

Deposit information

The phages carrying the inserted SEQ ID NO 1, i.e. phages clones B1, D1, F11 and N10 (see Figure 1) have been given the ECACC Accession numbers 99051922, 99051923, 99051924, and 99051925, respectively.

The cosmide carrying the inserted SEQ ID NO 2, i.e. cosmide pTY52 (see Figure 2) has been given the ECACC Accession number 99051926.

The depositions were made May 19, 1999.

Detailed description of the invention

The present invention is based on the finding that two fimbrial operons, the *saf* operon and the *tcf* operon, are specific for *Salmonella enterica* subspecies 1 bacteria. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as detection methods for *Salmonella enterica* subspecies I. The *saf* operon is specific for all *Salmonella enterica*

subspecies 1 bacteria and the *tcf* operon is specific for the serovar typhi of *Salmonella enterica* subspecies 1, see Examples 1 & 2.

The main object of the invention relates to two fimbrial operons, the *saf* operon and the *tcf* operon, that are specific for *Salmonella enterica subspecies* 1 bacteria for terapeutic use.

Another object of the present invention is to provide vaccines against *Salmonella enterica* subspecies 1 induced gastroentritis, entric fever and typhoid fever.

A further object of the present invention is to provide methods to detect *Salmonella enterica* subspecies 1. The nucleotide sequences according to the invention are useful for constructing vectors for use as vaccines for insertion into attenuated bacteria in constructing a recombinant vaccine, for insertion into a viral vector in constructing a recombinant viral vaccine, or for direct inoculation as a nucleic acid vaccine. The pili proteins according to the invention, or antigenic fragments thereof, can be used for active immunization and antibodies directed against them can be used for passive immunization. All these applications of the sequences according to the invention are obtained by applying standard techniques known to the man ordinary skilled in the art.

Vaccines against *Salmonella enterica* subspecies I.
The genes encoding the saf and tcf fimbrial structures, or fragments thereof, may be incorporated into a bacterial or viral vaccine comprising recombinant bacteria, virus or fungi which are engineered to produce one or more immunogenic epitopes of the saf or tcf fimbrial structures. In addition, the genes encoding the saf and tcf fimbrial structures, or part thereof, operatively linked to regulatory elements, can be introduced directly as a nucleic acid vaccine, to elicit a protective immune response.

The proteins or antigenic fragment thereof, deduced from the nucleic acid sequences of the present invention are useful alone or in conventional vaccine mixtures in the vaccine compositions according to the invention. The proteins could be produced by chemical synthesis or recombinant expression according to conventional methods.

The proteins and peptides according to the invention can be obtained by using a host organism transformed or transfected with an expression vector obtained by insertion of a gene according to the invention, or part thereof, into a vector in a conventional manner. The vector which is used to construct the expression vector is not particularly limited, but specific examples include plasmids such as pET (Stratagen) and the like; and phages such as M13 (NEB), phage display libraries and the like. As expression regulatory sequence can among others T7 promotors and lac promotors be used.

An appropriate host to be transformed or transfected with the expression vector can be chosen among for example *E.-coli, Salmonella* or *Bacillus subtilus*. The transformed or transfected host is cultured and proliferated under suitable conditions.

After culturing, the peptides of the present invention may be purified by, for example, chromatography, precipitation, and/or density gradient centrifugation. The thus obtained peptides can be used as a vaccine or for the production of antibodies directed against said peptides, which can be used for passive immunization.

The purified preparation containing one or several proteins according to the invention, or parts thereof, is then formulated as a pharmaceutical composition, as for example a vaccine, or in a mixture with adjuvants. If desired the proteins are fragmented by standard chemical or enzymatic techniques to produce antigenic segments.

In formulating the vaccine compositions with the peptide or protein, alone or in various combinations, the immunogen is adjusted to an appropriate concentration and formulated with any suitable vaccine adjuvant. The immunogen may also be incorporated into liposomes, or conjugated to polysaccharides and/or other polymers for use in a vaccine formulation.

The different vaccines according to the present invention are administered to mammals in many different ways. These include intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, oral, and intranasal routes of administration. The vaccine doses will differ depending on circumstances such

as body weight, interferences with other administered medicaments etc. The upper limit is not critical unless the dose shows toxicity.

The peptides and proteins of the present invention are also useful to produce monoclonal or polyclonal antibodies for use in passive immunotherapy against *Salmonella enterica* subspecies 1. Human immunoglobulin is preferred. Antisera is obtained from individuals immunized with proteins or peptides according to the invention. The immunoglobulin fraction is then enriched, for example by immunoaffininty or affininty chromatography. Antibodies raised in a suitable mammal or in the patient to be treated, can subsequently be administered locally or topically, e.g. orally to the patient.

Detection of *Salmonella enterica* subspecies I in general.
The sequences according to the invention, or part thereof, or fragments hybridizing therewith, as well as the proteins according to the invention, or part thereof, and antibodies directed to said proteins, or antigenic fragments thereof, can be used in molecular diagnostic assays for the detection of *Salmonell enterica* subspecies I.

Nucleic acids having the nucleotide sequence according to the invention, or any nucleotide sequence hybridizing therewith can be used as a probe in nucleic acid hybridization assays for the detection of *Salmonella spp* in various tissues and body fluids of patients. The hybridization assay may be of any type including; Southern blots, Northern blots, colony blots.

PCR technology is the most preferred technology for detection according to the invention of *Salmonella enterica* subspecies 1. Primers of at least one selected from the 5' end and one from the 3' end can be used in PCR and other known tests to rapidly identify the presence of *Salmonella enterica* subspecies 1. This is according to conventional techniques.

The isolated and purified proteins and peptides of the invention can be used as diagnostics to measure an increase in serum titer of *Salmonella enterica* subspecies I-specific antibody since they bind strongly to these antibodies. A serum test sample can be screened for *Salmonella enterica* subspecies I by methods such as for example ELISA.

The invention further comprises the use of antibodies directed against the saf and tcf fimbrie structures for quantitative or qualitative determinations of the pili proteins of the invention, or fractions thereof, in cells, tissues or body fluids.

Detection of *Salmonella enterica* subspecies I by using nucleic acid hybridization technology

Nucleic acid hybridization technology can also be to detect *Salmonella enterica* subspecies 1 according to the invention. The nucleic acid probes chosen from parts of the sequences according to the invention can be either DNA or RNA. DNA sequences complementary to the sequences according to the invention can also be used. The binding of the probe to the target sequence, i.e. the hybridization, must not be perfect. Variations and mutations of the sequences according to the invention can be used as long as they hybridize good enough to detect *Salmonella enterica* subspecies I. The preferred length of the nucleic acid probes is about 10 to 400 nucleotides, most preferred not longer than 100 nucleotides.

The nucleotide probe is preferably chosen from the parts of the sequences that have the least variation. In the most preferred embodiments when screening for SEQ ID NO 1 (the *saf* operon, specific for *Salmonella enterica* subspecies 1) a nucleotide probe or PCR primer selected from nucleotides 37 368-37 868 should be avoided since this region is hypervariable.

The nucleic acid probes according to the invention are prepared by any conventional method such as organic synthesis, recombinant techniques, or isolation from genomic DNA.

The nucleic acid probes of the invention are labeled in a conventional manner to signal hybridization to target nucleic acid from *Salmonella enterica* subspecies I. The labeling may comprise a radiolabel, an enzyme, a bacterial label, a fluorescent label, an antibody, an antigen, a latex particle, an electron dense compound, or a light scattering particle.

The probes may be provided in a lyophilized form, to be reconstituted in a buffer appropriate for hybridization, or the probes may already be present in

such a buffer. The buffer may contain a suitable hybridization enhancer, detergent, carrier DNA, and a compound to increase the specificity.

Any conventional hybridization assay technique, such as dot blot hybridization, Southern blotting, sandwich hybridization, displacement hybridization and the like, can be used.

The target analyte polynucleotide of a microorganism may be in various media, most often in a biological, or physiological specimen. In most cases it is preferred to subject the specimen containing the target polynucleotide to any conventional extraction, purification, and/or isolation before conducting the analysis.

The sample containing the target analyte nucleotide sequence must often be treated to convert the DNA to a single-stranded form, which may be accomplished by a variety of conventional techniques, such as thermal or chemical techniques.

The following examples describe the isolation and specificity of the sequences according to the invention.

EXAMPLE 1

Identification and characterization of the *saf* operon.

The present inventors found, upon investigation of a 7 kb chromosomal region on centisome 7 originally isolated from the *S. typhimurium* strain SR-11 $_K$3181, a region that exhibits many of the traits that define a pathogenicity island. It has a lower G+C composition than the average composition of the *Salmonella* genome and includes many sequences related to different mobile genetic elements. The region is not present in *E.coli* K12, and the *Salmonella* specific DNA is inserted between the tRNA gene *aspV* and the stop codon of *yafV*, a hypothetical protein upstream of the *yafH* gene at 5 min in the *E.coli* chromosome. This *Salmonella* specific insert encodes proteins creating adhesive structures and other virulence factors. Sequencing revealed genes encoding a new fimbrial operon that they designated *Salmonella* Atypical Fimbriae (*saf*), due to its relatedness to a subgroup of adhesive structures forming thin atypical fimbriae or non-fimbrial adhesins.

The *saf* operon consists of four contiguous genes, *safA*, *safB*, *safC* and *safD* that encode fimbrial subunit, periplasmic chaperone, outer membrane usher protein and alternative fimbrial subunit, respectively. The genes *safA, B, C* and *safD* encode putative proteins of 166, 244, 836 and 156 amino acids, respectively. Analyzes of clinical *Salmonella* isolates showed that DNA of 195 out of 198 clinical isolates belonging to *S. enterica* subspecies I hybridized with *safB* and *safC*, i.e. these sequences are common to more than 99% of the known *Salmonella enterica* subspecies 1 bacteria. The inventors showed that 58% of these clinical isolates carry the *safA*, see Table 1.

Table 1. The prevalence of the *saf* genes in clinical *Salmonella* isolates.

Serovar	*safA*	*safB*	*safC*	# isolates
S. adelaide	-	+	+	1
S. agona	+	+	+	6
S. anatum	-	+	+	3
S. bareilly	+	+	+	3
S. blockley	+	+	+	3
S. bovismorbificans	-	+	+	5
S. braenderup	-	+	+	4
S. brandenburg	+	+	+	1
S. bredeney	+/-	+	+	15
S. chester	+	+	+	1
S. colindale	-	+	+	1
S. derby	-	+	+	1
S. dublin	-	+	+	1
S. eastbourne	+	+	+	2
S. emek	+	+	+	1
S. enteritidis	-	+	+	8
S. give	-	+	+	1
S. goettingen	+	+	+	1
S. haardt	-	+	+	1
S. hadar	+	+	+	16
S. heidelberg	-	+	+	1
S. hvittingfoss	+	+	+	5
S. infantis	-/+	+	+	6
S. java	-	+	+	1
S. javiana	-	+	+	1
S. kottbus	-	+	+	1
S. livingstone	-	+	+	1
S. london	+	+	+	1
S. maastricht	+	+	+	2
S. mbandaka	-	-	-	3
S. montevideo	+	+	+	1
S. muenster	-	+	+	1
S. newport	+	+	+	2
S. ohio	+	+	+	1
S. oranienburg	+	+	+	2
S. panama	+	+	+	3
S. potsdam	+	+	+	1
S. rissen	-	-	-	1
S. saarbrucken	-	+	+	1
S. saint paul	+	+	+	3
S. schwartzengrund	-	+	+	1
S. singapore	+	+	+	1
S. stanley	+	+	+	5
S. subsp I 4.5,12:-:-	+	+	+	2
S. subsp I 4.5,12:b:-	-	+	+	1
S. subsp I 4.5,12:i:-	+	+	+	1
S. subsp I spont	-	+	+	1
S. tennessee	+	+	+	2
S. thompson	-	+	+	1
S. typhi	-	+	+	1
S. typhimurium	+	+	+	27
S. virchow	+	+	+	7
S. weltervreden	-	+	+	1
S. worthington	-	-	-	2
S. subsp III	-	-	-	1

The phylogenetic distribution of the identified genes on the cs7 insert was investigated using the well defined SARC collection, which showed that the presence of the *safA, safB, safC* and *safD* genes is restricted to *S. enterica* subspecies I (Fig. 3). This region is hence the first subspecies I specific genetic region to be identified with a broad distribution within the subspecies. Since the serovars of subspecies I constitute over 99% of human salmonellosis and are preferentially associated with warm blooded animals, it implicates a role for the *saf* adhesive organelle in the colonization of these organisms.

EXAMPLE 2

Identification and characterization of the *tcf* operon.

The present inventors found that *Salmonella enterica* subspecies I serovar Typhi contains DNA encoding an additional fimbrial operon, the tcf operon, in the *sinR-pagN* intergenic region. Southern blot analysis revealed a markedly different restriction pattern in *S. enterica* serovar Typhi than the other subspecies I isolates, suggesting that the *saf-sin* region in serovar Typhi might carry additional DNA relative to serovar Typhimurium strains. A PCR reaction (using a kit from Roche) was therefore performed using a *sinR* (5'-GTA AAT CGC TTA GTC GCC-3') specific forward primer and a *pagN* (5'-TCA ACT CAA CCT TCA GCC-3') specific reverse primer.

This primer pair produced, as expected, a product of 2 kb in serovar Typhimurium from the SARC collection, while from serovar Typhi the product was 10 kb. Thus, the neighboring *sinR* and *pagN* genes in serovar Typhimurium strains are separated by approximately 8 kb in serovar Typhi.

The Typhi specific PCR product was purified, digested partially with *EcoRI* and sub-cloned into pUC18 forming a set of overlapping clones. Sequencing of the clones revealed a putative fimbrial operon designated *tcf* for Typhi Colonizing Factor. Four ORFs, *tcfA,B,C,D*, have been identified with putative proteins having significant homology to CooB (38% identical over 192 aa), CooA (37% identical over 170 aa), CooC (34% identical over 872 aa) and CooD (31% identical over 272 aa), respectively. The Coo proteins are involved in the biosynthesis of the CS1 colonizing factor antigens of enterotoxigenic *E.coli* (Fig. 4) (Froehlich et al., 1994). The peptide of the *tcfB* ORF is also homologous to the CblA major fimbrial subunit protein (45% identical over 154 aa) of the cable

type II pili of the cystic fibrosis-associated *Burkholderia cepacia*(Sajjan et al., 1995). Down-stream of the *tcf*-operon two ORFs were identified with the same transcriptional orientation as the *tcf* genes. The first was designated *tinR* for Typhi insert regulator because it is homologous (33% identical over 144 aa) to AzlB of *Bacillus subtilis*, a member of the Lrp/AsnC family of transcriptional regulators (Belitsky et al., 1997). *tinR* is followed by an ORF (*tioA* for Typhi insert orf) encoding a putative protein of 205 amino acids with no significant homologies to anything in the DDBJ/EMBL/GenBank databases. The above sequence from *Salmonella enterica* serovar Typhi strain RKS 3333 and the *tcf* region of the incomplete genome sequence from serovar Typhi strain CT18 (http:// www.sanger.ac.uk) are 99% identical over the total length of the investigated region in concordance with the clonal nature of the serovar .

A 2 kb large internal *Eco*R I fragment was used as a probe in a Southern blot of the SARC collection. This blot shows that *Salmonella enterica* subspecies I serovar Typhi (SARC2) is the only strain in the collection possessing DNA hybridizing to this fragment (Fig. 4).

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Claims:

1. Peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.

2. Antibodies directed against a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.

3. Nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.

4. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1), or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.

5. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 2 (SEQ ID NO 2), or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.

6. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and, optionally, a pharmaceutically acceptable carrier.

7. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2) and, optionally, a pharmaceutically acceptable carrier.

8. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1), has been inserted and, optionally, a pharmaceutically acceptable carrier.

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9. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2), has been inserted and, optionally, a pharmaceutically acceptable carrier.

10. A method for protection against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to any of claims 4, 6, and 8.

11. A method for protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to any of claims 5, 7, and 9.

12. Antibodies directed against a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

13. Peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

14. Primers for, or probes that hybridize with, a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method for the purpose of detecting *Salmonella enterica* subspecies I.

Claims:

1. Peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.

2. Antibodies directed against a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.

3. Nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.

4. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1), or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.

5. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 2 (SEQ ID NO 2), or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.

6. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and, optionally, a pharmaceutically acceptable carrier.

7. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2) and, optionally, a pharmaceutically acceptable carrier.

8. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1), has been inserted and, optionally, a pharmaceutically acceptable carrier.

9. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2), has been inserted and, optionally, a pharmaceutically acceptable carrier.

10. A method for protection against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to any of claims 4, 6, and 8.

11. A method for protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to any of claims 5, 7, and 9.

12. Antibodies directed against a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

13. Peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

14. Primers for, or probes that hybridize with, a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

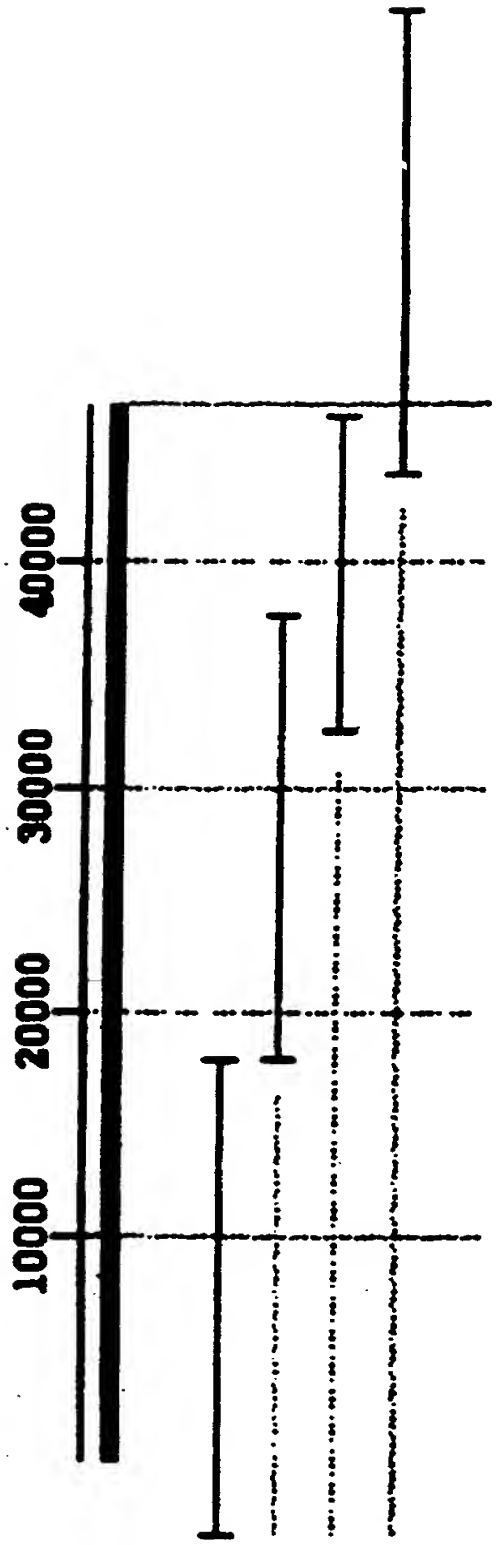

Fig. 1

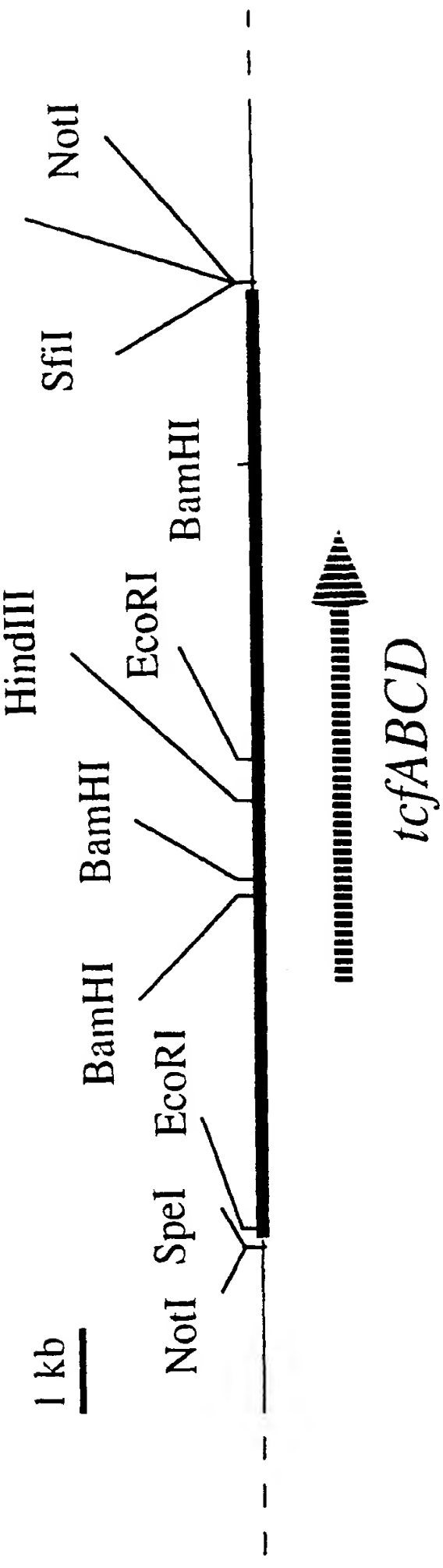
SwaI
NotI
SfiI
BamHI
EcoRI
HindIII
BamHI
tcfABCD
BamHI
EcoRI
NotI
SpeI
1 kb

Fig. 2

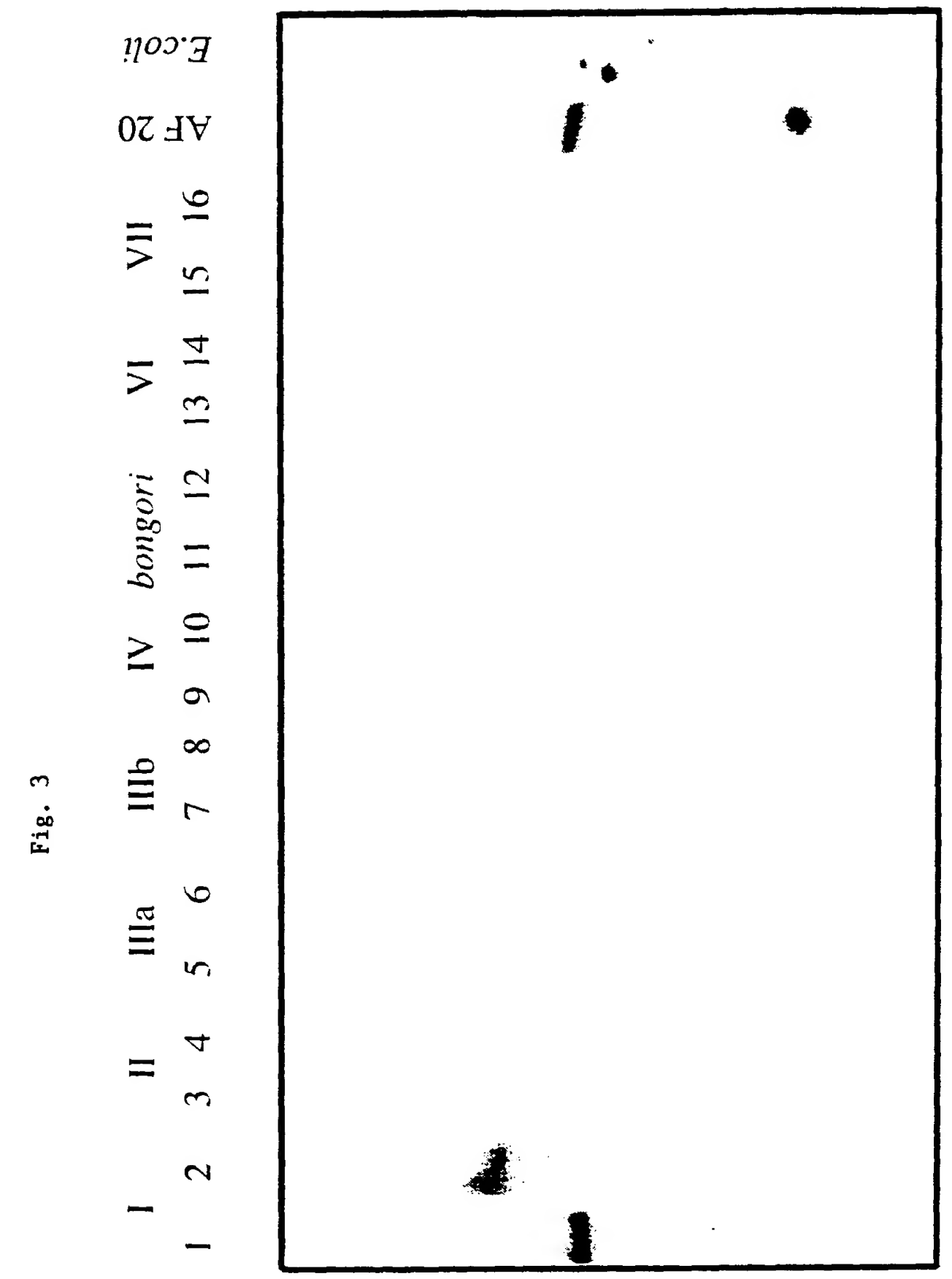
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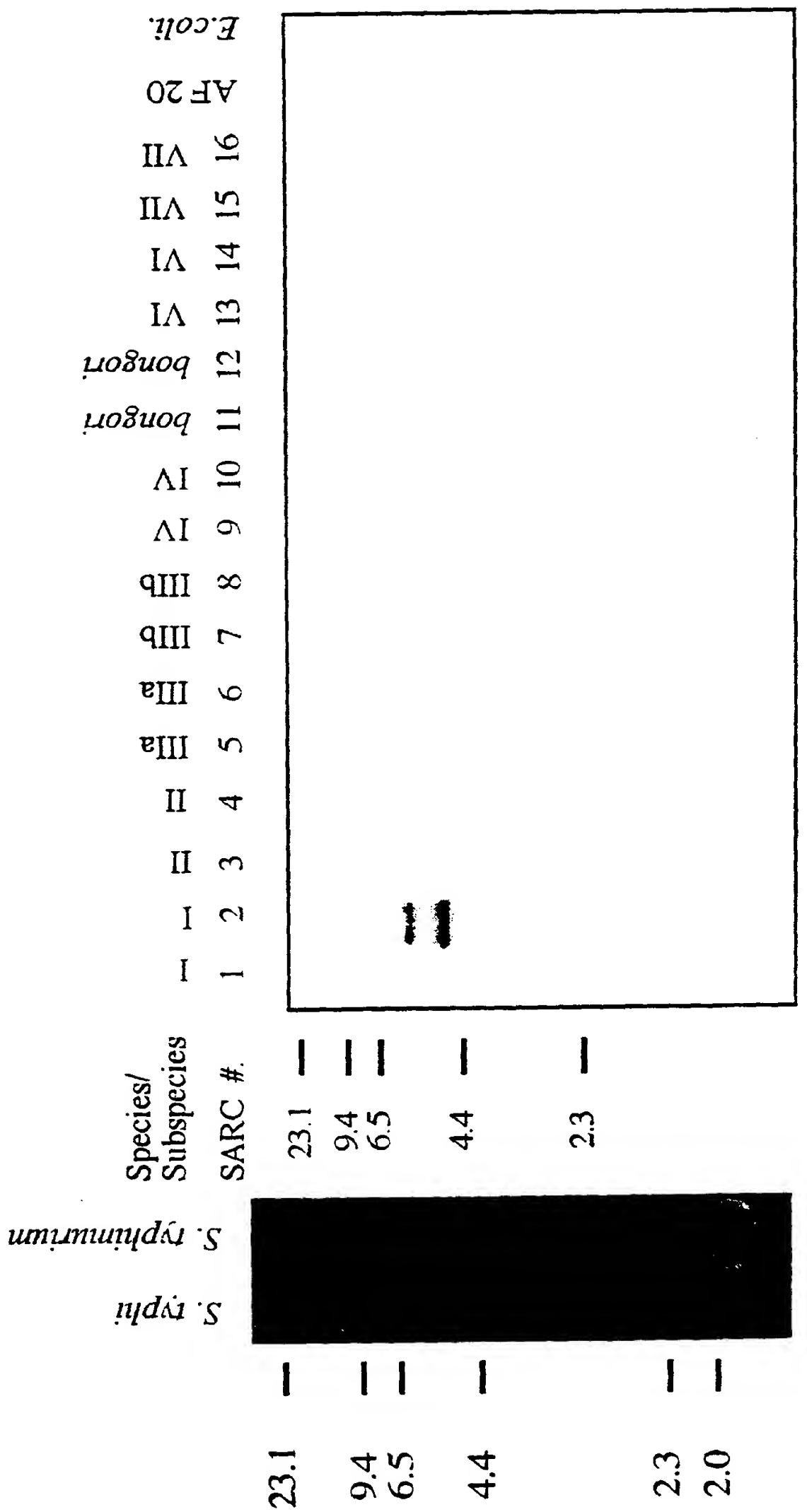
Fig. 3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VI 14
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II 3
I 2
I 1
Species/ Subspecies
SARC #.
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9.4
6.5
4.4
2.3
S. typhimurium
S. typhi
23.1
9.4
6.5
4.4
2.3
2.0

Fig. 4

of respective phage insert is represented by horizontal bars. Name and size of the phage inserts are indicated on the left side of the figure.

Figure 2.

Schematic representation of the pTY52 cosmid comprising the *tcf*-operon (SEQ ID NO 2).

A *tcf* specific PCR fragment of 11105 bp was cloned into the Expand vector I cosmid (Roche). The insert is represented with a thick black line while vector sequences are represented with thin lines. Relevant restriction sites sequences are indicated. The position of the *tcf*-operon, i.e. *tcfA, B, C* and *D* (SEQ ID NO 2), is represented by a shaded arrow.

Figure 3.

The phylogenetic distribution of the identified genes on the cs7 insert was investigated using the well defined SARC collection, see Example 1.

Figure 4.

A 2 kb large internal *Eco*R I fragment was used as a probe in a Southern blot of the SARC collection, see Example 2.

Sequence listing

SEQ ID NO 1—DNA sequence of the genes encoding the precursor of the saf fimbrie unit of *Salmonella enterica* subspecies I.

SEQ ID NO 2—DNA sequence of the genes which encode the precursor of the tcf fimbrie unit of *Salmonella enterica* subspecies I serovar Typhi.

Deposit information

The phages carrying the inserted SEQ ID NO 1, i.e. phages clones B1, D1, F11 and N10 (see Figure 1) have been given the ECACC Accession numbers 99051922, 99051923, 99051924, and 99051925, respectively.

The cosmide carrying the inserted SEQ ID NO 2, i.e. cosmide pTY52 (see Figure 2) has been given the ECACC Accession number 99051926.

The depositions were made May 19, 1999.

Detailed description of the invention

The present invention is based on the finding that two fimbrial operons, the *saf* operon and the *tcf* operon, are specific for *Salmonella enterica* subspecies 1 bacteria. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as detection methods for *Salmonella enterica* subspecies I. The *saf* operon is specific for all *Salmonella enterica*

Claims:

1. Protein encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO 1 and SEQ ID NO 2, or parts thereof, for use in medicine.

2. Antibodies directed against the protein encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO 1 and SEQ ID NO 2, or antigenic fragments thereof for use in medicine.

3. Nucleotide sequence selected from the group consisting of SEQ ID NO 1 and SEQ ID NO 2, or parts thereof, for use in medicine.

4. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising the protein, or parts thereof, encoded by the nucleotide sequence according to SEQ ID NO 1 or antibodies directed against the protein encoded by SEQ ID NO 1, or antigenic fragments thereof and, optionally, a pharmaceutically acceptable carrier.

5. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising the protein, or parts thereof, encoded by the nucleotide sequence according to SEQ ID NO 2 or antibodies directed against the protein encoded by SEQ ID NO 2, or antigenic fragments thereof and, optionally, a pharmaceutically acceptable carrier.

6. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising SEQ ID NO 1, or parts thereof and, optionally, a pharmaceutically acceptable carrier.

7. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising SEQ ID NO 2, or parts thereof and, optionally, a pharmaceutically acceptable carrier.

8. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a host in which a recombinant vector comprising SEQ ID NO 1, or parts thereof, has been inserted and, optionally, a pharmaceutically acceptable carrier.

9. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a host in which a recombinant vector comprising SEQ ID NO 2, or parts thereof, has been inserted and, optionally, a pharmaceutically acceptable carrier.

10. A method for protection against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to any of claims 4, 6, and 8.

11. A method for protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to any of claims 5, 7, and 9.

12. Antibodies directed against the protein encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO 1 and SEQ ID NO 2, or antigenic fragments thereof, for use in a diagnostic method.

13. Protein encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO 1 and SEQ ID NO 2, or parts thereof, for use in a diagnostic method.

14. Primers for or, probes that hybridize with a nucleotide sequence selected from the group consisting of SEQ ID NO 1 and SEQ ID NO 2, for use in a diagnostic method.

SEQUENCE LISTING NO. 1

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attaatgtgc catgttcacg gggaggttgt gcgacgtttg cataatccag caagaactga 36780

aaggaagggg agagcttttt catgcctgta taatcagtct ggcctgtgtc agtcagctct 36840

tagtgttgag actctcgttg gagcgttata attgcttttc tgtttcggaa aacaagattt 36900

tccattaaag atcttccctg cgaggaaaag ttaactaata atcttaccgt cgagttagga 36960

gatgtatgtt taaatataaa caatgttgca acgatgcctg ataattatcc tctcttcgaa 37020

gataagtttc ccacacccag tgtagtaggt gtcatggtaa tgttatcact tgaatgtaaa 37080

tggaaggtat aattgctttt tgactggcat tctattccac cctgacaaca cgatgttaac 37140

atcaacactg tttatattgg caataacgca atttttttca gattaagagg tgctctgata 37200

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tatagatttt tatgacatta cttatttgaa ttggtaacaa ataccaataa gtacaagctg 37260

ttattaccag ccacggattt tttacatacg gtaagatttg gtatggcgtt atgtattctg 37320

gatgtgctgg attatttttaa tttggtttaa aaaaggtggt tattcaa atg aaa agc   37376
                                                      Met Lys Ser
                                                        1

ata aaa aaa ttg att atc gca agt gcg ttg agc atg atg gct gct agt   37424
Ile Lys Lys Leu Ile Ile Ala Ser Ala Leu Ser Met Met Ala Ala Ser
      5                  10                  15

tgt tat gct ggc tca ttt ttg ccg aac tca gag caa caa aaa tca gtg   37472
Cys Tyr Ala Gly Ser Phe Leu Pro Asn Ser Glu Gln Gln Lys Ser Val
 20                  25                  30                  35

gat att gtg ttt tcc tct ccc caa gat tta acc gta tcg ctt att cca   37520
Asp Ile Val Phe Ser Ser Pro Gln Asp Leu Thr Val Ser Leu Ile Pro
                 40                  45                  50

gtg tcg ggc tta aag gct ggg aaa aat gct cct agc gcg aaa att gcg   37568
Val Ser Gly Leu Lys Ala Gly Lys Asn Ala Pro Ser Ala Lys Ile Ala
            55                  60                  65

aag ctt gta gtt aat tct act act ctt aaa gaa ttc ggg gtc agg ggg   37616
Lys Leu Val Val Asn Ser Thr Thr Leu Lys Glu Phe Gly Val Arg Gly
        70                  75                  80

att tct aac aac gtg gta gac agt act ggc act gca tgg cgt gta gct   37664
Ile Ser Asn Asn Val Val Asp Ser Thr Gly Thr Ala Trp Arg Val Ala
     85                  90                  95

ggt aaa aat act ggt aaa gag atc ggt gtg ggc tta tca agt gac agt   37712
Gly Lys Asn Thr Gly Lys Glu Ile Gly Val Gly Leu Ser Ser Asp Ser
100                 105                 110                 115

ctt aga aga tct gat agc acg gaa aaa tgg aat ggg gtg aac tgg atg   37760
Leu Arg Arg Ser Asp Ser Thr Glu Lys Trp Asn Gly Val Asn Trp Met
                120                 125                 130

acc ttt aat agc aat gac aca ctt gat att gtc ctg aca gga ccg gcg   37808
Thr Phe Asn Ser Asn Asp Thr Leu Asp Ile Val Leu Thr Gly Pro Ala
            135                 140                 145

cag aat gtc aca gct gac acg tac cca ata act tta gac gta gtg gga   37856
Gln Asn Val Thr Ala Asp Thr Tyr Pro Ile Thr Leu Asp Val Val Gly
        150                 155                 160

tat caa cct taa tagtaaacaa ctattagtgt attgtgcctt gtttaaggcg       37908
Tyr Gln Pro
    165

caatacacat caaatcatct atttttcttt tacaattttt gat atg aaa ata gtt   37963
                                               Met Lys Ile Val
                                                       170

aat ttt gct gta atg gcg gta gct ttg ttc gcc act aat tct atg gtt   38011
Asn Phe Ala Val Met Ala Val Ala Leu Phe Ala Thr Asn Ser Met Val
            175                 180                 185
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tca gta tat gcc gtc aac cag caa tta aat tca gcc act aaa tta ttc   38059
Ser Val Tyr Ala Val Asn Gln Gln Leu Asn Ser Ala Thr Lys Leu Phe
        190                 195                 200

agc gtg aag ctg ggg gct aca cga gtg att tat cac gct ggt acg gct   38107
Ser Val Lys Leu Gly Ala Thr Arg Val Ile Tyr His Ala Gly Thr Ala
    205                 210                 215

gga gcg acg ctc tcg gtg agc aac ccg cag aat tac cct att ttg gtt   38155
Gly Ala Thr Leu Ser Val Ser Asn Pro Gln Asn Tyr Pro Ile Leu Val
220                 225                 230                 235

cag tct tca gtc aaa gca gca gac aaa agt tcg cct gct ccc ttt ttg   38203
Gln Ser Ser Val Lys Ala Ala Asp Lys Ser Ser Pro Ala Pro Phe Leu
                240                 245                 250

gtg atg ccg cct cta ttt cgt tta gaa gca aac cag cag agt caa ctg   38251
Val Met Pro Pro Leu Phe Arg Leu Glu Ala Asn Gln Gln Ser Gln Leu
            255                 260                 265

cgt att gtc cgt act ggt ggt gac atg cca acg gat cgt gag act tta   38299
Arg Ile Val Arg Thr Gly Gly Asp Met Pro Thr Asp Arg Glu Thr Leu
        270                 275                 280

cag tgg gtc tgt ata aag gcg gta cca ccc gaa aat gaa ccg tcg gat   38347
Gln Trp Val Cys Ile Lys Ala Val Pro Pro Glu Asn Glu Pro Ser Asp
    285                 290                 295

aca cag gct aag ggc gcg acc ctt gac ctc aat ttg tcc atc aac gcc   38395
Thr Gln Ala Lys Gly Ala Thr Leu Asp Leu Asn Leu Ser Ile Asn Ala
300                 305                 310                 315

tgt gat aag ctg att ttc cgc ccg gat gcc gtg aag ggg acg ccg gaa   38443
Cys Asp Lys Leu Ile Phe Arg Pro Asp Ala Val Lys Gly Thr Pro Glu
                320                 325                 330

gat gtt gca gga aat tta aga tgg gtg gag acg ggc aac aaa ctt aag   38491
Asp Val Ala Gly Asn Leu Arg Trp Val Glu Thr Gly Asn Lys Leu Lys
            335                 340                 345

gtg gag aac ccc acc ccg ttt tac atg aat tta gcc tct gtc aca gta   38539
Val Glu Asn Pro Thr Pro Phe Tyr Met Asn Leu Ala Ser Val Thr Val
        350                 355                 360

ggg gga aag ccc att aca ggg ctt gag tat gtc ccc ccc ttt gct gac   38587
Gly Gly Lys Pro Ile Thr Gly Leu Glu Tyr Val Pro Pro Phe Ala Asp
    365                 370                 375

aaa aca cta aat atg cca ggt agt gcc cat ggt gat atc gag tgg aga   38635
Lys Thr Leu Asn Met Pro Gly Ser Ala His Gly Asp Ile Glu Trp Arg
380                 385                 390                 395

gtt att aca gac ttt ggt ggt gaa agt cat ccg ttc cac tac gtt ctt   38683
Val Ile Thr Asp Phe Gly Gly Glu Ser His Pro Phe His Tyr Val Leu
                400                 405                 410

aaa taa atccaggggc ttagcggcag aaa atg aag ttc aaa caa cct gcc ttg 38736
Lys                                 Met Lys Phe Lys Gln Pro Ala Leu
                                        415                 420

cta ctg ttc atc gcg gga gtg gtt cat tgc gca aat gcg cac act tac   38784
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Leu Leu Phe Ile Ala Gly Val Val His Cys Ala Asn Ala His Thr Tyr
            425                 430                 435

aca ttc gat gca tca atg ttg ggc gat gca gcg aaa ggg gtt gat atg   38832
Thr Phe Asp Ala Ser Met Leu Gly Asp Ala Ala Lys Gly Val Asp Met
        440                 445                 450

tcg ctc ttt aac cag ggg tta caa cag cca ggg act tat cgc gtg gac   38880
Ser Leu Phe Asn Gln Gly Leu Gln Gln Pro Gly Thr Tyr Arg Val Asp
    455                 460                 465

gtg atg gtg aat ggt aaa cgt gtc gac acc cgt gat gtg gtg ttc aaa   38928
Val Met Val Asn Gly Lys Arg Val Asp Thr Arg Asp Val Val Phe Lys
470                 475                 480                 485

ttg gaa aag gat ggg caa gga acg cct gtt ctg gct cct tgt ttg acg   38976
Leu Glu Lys Asp Gly Gln Gly Thr Pro Val Leu Ala Pro Cys Leu Thr
                490                 495                 500

gtc agt cag ctt tca cgc tac ggc gta aaa acg gaa gat tac cct cag   39024
Val Ser Gln Leu Ser Arg Tyr Gly Val Lys Thr Glu Asp Tyr Pro Gln
            505                 510                 515

ttg tgg aaa gca gca aag ccc cca gat gag tgt gcg gat ctg acc gcc   39072
Leu Trp Lys Ala Ala Lys Pro Pro Asp Glu Cys Ala Asp Leu Thr Ala
        520                 525                 530

att cca cag gct aaa gcg gta ctg gat atc aat aat cag caa ctg caa   39120
Ile Pro Gln Ala Lys Ala Val Leu Asp Ile Asn Asn Gln Gln Leu Gln
    535                 540                 545

ctg agt att ccg cag ttg gcg ttg cgt ccg gaa ttt aag ggg atc gct   39168
Leu Ser Ile Pro Gln Leu Ala Leu Arg Pro Glu Phe Lys Gly Ile Ala
550                 555                 560                 565

cca gaa gat ctt tgg gat gat ggt att ccg gcg ttt ctg atg aac tac   39216
Pro Glu Asp Leu Trp Asp Asp Gly Ile Pro Ala Phe Leu Met Asn Tyr
                570                 575                 580

agt gcg agg aca acg cag acg gat tac aaa atg gat atg gtg ggg cgt   39264
Ser Ala Arg Thr Thr Gln Thr Asp Tyr Lys Met Asp Met Val Gly Arg
            585                 590                 595

gac aac tct tcc tgg gta caa ctg caa ccg gga atc aat ata ggt gcg   39312
Asp Asn Ser Ser Trp Val Gln Leu Gln Pro Gly Ile Asn Ile Gly Ala
        600                 605                 610

tgg cgt gtc cgc aat gcg acc agc tgg cag cgg agt agt caa ctg tcg   39360
Trp Arg Val Arg Asn Ala Thr Ser Trp Gln Arg Ser Ser Gln Leu Ser
    615                 620                 625

ggg aag tgg cag gca gca tat acc tat gct gag cgt gga ctg tac tca   39408
Gly Lys Trp Gln Ala Ala Tyr Thr Tyr Ala Glu Arg Gly Leu Tyr Ser
630                 635                 640                 645

cta aaa agt cgt ctg act ctg ggg caa aag act tcg cag ggg gag ata   39456
Leu Lys Ser Arg Leu Thr Leu Gly Gln Lys Thr Ser Gln Gly Glu Ile
                650                 655                 660

ttt gat agt gtg cca ttt acc ggt gtg atg ttg gca tcg gat gac aac   39504
Phe Asp Ser Val Pro Phe Thr Gly Val Met Leu Ala Ser Asp Asp Asn
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                665                 670                 675

atg gtg ccc tac agt gag cgg cag ttt gct ccg gta gtg cgt ggg att   39552
Met Val Pro Tyr Ser Glu Arg Gln Phe Ala Pro Val Val Arg Gly Ile
        680                 685                 690

gcc cgc acg cag gct cgg gtg gag gtc aaa cag aat ggt tac acc att   39600
Ala Arg Thr Gln Ala Arg Val Glu Val Lys Gln Asn Gly Tyr Thr Ile
    695                 700                 705

tac aac acc act gtg gcg ccc gga ccg ttt gca ctg cgg gat ctg tcg   39648
Tyr Asn Thr Thr Val Ala Pro Gly Pro Phe Ala Leu Arg Asp Leu Ser
710                 715                 720                 725

gta aca gac agt agt ggt gat ctg cat gtc acc gtg tgg gag gcc gat   39696
Val Thr Asp Ser Ser Gly Asp Leu His Val Thr Val Trp Glu Ala Asp
                730                 735                 740

ggc agt aca caa atg ttt gtg gtg ccg tat cag acc ccg gcg ata gca   39744
Gly Ser Thr Gln Met Phe Val Val Pro Tyr Gln Thr Pro Ala Ile Ala
            745                 750                 755

ctg cac cag gga tat ttg aag tac agc ctg ttg gcg ggc cga tac cga   39792
Leu His Gln Gly Tyr Leu Lys Tyr Ser Leu Leu Ala Gly Arg Tyr Arg
        760                 765                 770

tcg tca gac tct gca acg gat aag cgg cag atc gcg cag gct acg ttg   39840
Ser Ser Asp Ser Ala Thr Asp Lys Arg Gln Ile Ala Gln Ala Thr Leu
    775                 780                 785

atg tat ggt ctg ccg tgg aat ctc act gca tac ggc ggt ata cag agt   39888
Met Tyr Gly Leu Pro Trp Asn Leu Thr Ala Tyr Gly Gly Ile Gln Ser
790                 795                 800                 805

gca acg cat aat caa gct gca ttg ctt ggt ttg ggg gga tct ctc ggg   39936
Ala Thr His Asn Gln Ala Ala Leu Leu Gly Leu Gly Gly Ser Leu Gly
                810                 815                 820

cgg tgg ggg agt tta tct gtc gat gga agc gac aca cac agt cag cgt   39984
Arg Trp Gly Ser Leu Ser Val Asp Gly Ser Asp Thr His Ser Gln Arg
            825                 830                 835

cag ggg gag gcg gta cag caa gga gcc tcc tgg cga ctg cgt tac agc   40032
Gln Gly Glu Ala Val Gln Gln Gly Ala Ser Trp Arg Leu Arg Tyr Ser
        840                 845                 850

aac cag ctg act gcg acg ggg aca aat ttt ttt ctg acg aga tgg cag   40080
Asn Gln Leu Thr Ala Thr Gly Thr Asn Phe Phe Leu Thr Arg Trp Gln
    855                 860                 865

tat gcc tcg cag ggc tat aac acc cta tcc gat gtg ctc gac agt tat   40128
Tyr Ala Ser Gln Gly Tyr Asn Thr Leu Ser Asp Val Leu Asp Ser Tyr
870                 875                 880                 885

cga cat aat ggc aac cgt cta tgg tcg tgg cgg gaa aat ttg cag ccg   40176
Arg His Asn Gly Asn Arg Leu Trp Ser Trp Arg Glu Asn Leu Gln Pro
                890                 895                 900

agc tcg cgt act acc ctg atg ttg agt cag tca tgg ggg agg cat ttg   40224
Ser Ser Arg Thr Thr Leu Met Leu Ser Gln Ser Trp Gly Arg His Leu
            905                 910                 915
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ggc aat ctg agt tta acc ggt tcc cgt acc gac tgg cgt aat cgc ccc   40272
Gly Asn Leu Ser Leu Thr Gly Ser Arg Thr Asp Trp Arg Asn Arg Pro
        920                 925                 930

ggt cat gat gac agc tac gga ctg agt tgg gga acc tct atc gga ggg   40320
Gly His Asp Asp Ser Tyr Gly Leu Ser Trp Gly Thr Ser Ile Gly Gly
    935                 940                 945

ggc tcg ctg tca ttg aac tgg aat caa aac aga acg ctg tgg cgc aat   40368
Gly Ser Leu Ser Leu Asn Trp Asn Gln Asn Arg Thr Leu Trp Arg Asn
950                 955                 960                 965

ggc gcg cac cgt aaa gag aac ata acc agc ctg tgg ttc agt atg cca   40416
Gly Ala His Arg Lys Glu Asn Ile Thr Ser Leu Trp Phe Ser Met Pro
                970                 975                 980

tta agc cgc tgg acg ggg aat aat gta agt gct agt tgg cag atg act   40464
Leu Ser Arg Trp Thr Gly Asn Asn Val Ser Ala Ser Trp Gln Met Thr
            985                 990                 995

tca cca tca cac ggt ggt cag acg caa caa gtg ggg gtc aac gga gag   40512
Ser Pro Ser His Gly Gly Gln Thr Gln Gln Val Gly Val Asn Gly Glu
       1000                1005                1010

gca ttc agt cag caa ctg gat tgg gag gtg cgt cag agt tac cgt gcc   40560
Ala Phe Ser Gln Gln Leu Asp Trp Glu Val Arg Gln Ser Tyr Arg Ala
   1015                1020                1025

gat gcc ccg cca ggt ggt ggt aat aac agc gca ttg cac ttg gca tgg   40608
Asp Ala Pro Pro Gly Gly Gly Asn Asn Ser Ala Leu His Leu Ala Trp
1030                1035                1040                1045

aat ggg gat tac ggc ctg tta ggt ggt gac tat agc tac agc cgg gcg   40656
Asn Gly Asp Tyr Gly Leu Leu Gly Gly Asp Tyr Ser Tyr Ser Arg Ala
                1050                1055                1060

atg cgc cag atg gga gtc aat atc gcg gga ggt ata gtt atc cac cat   40704
Met Arg Gln Met Gly Val Asn Ile Ala Gly Gly Ile Val Ile His His
            1065                1070                1075

cat ggt gtg acg ctg ggg caa cct ttg caa ggc tca gtg gcg ctg gtt   40752
His Gly Val Thr Leu Gly Gln Pro Leu Gln Gly Ser Val Ala Leu Val
       1080                1085                1090

gaa gcg cca ggg gcc tcg ggg gtg cca gtt ggc ggc tgg cct ggc gtt   40800
Glu Ala Pro Gly Ala Ser Gly Val Pro Val Gly Gly Trp Pro Gly Val
   1095                1100                1105

aag acg gat ttt cgt ggc gac acc aca gtg ggc aac ctg aac gtc tat   40848
Lys Thr Asp Phe Arg Gly Asp Thr Thr Val Gly Asn Leu Asn Val Tyr
1110                1115                1120                1125

cag gag aat aca gtc agc ctc gat ccg tcg cga cta ccg gat gac gca   40896
Gln Glu Asn Thr Val Ser Leu Asp Pro Ser Arg Leu Pro Asp Asp Ala
                1130                1135                1140

gag gtc aca caa acc gat gtg cgc gtg gtg cca acc gaa ggg gcg gtg   40944
Glu Val Thr Gln Thr Asp Val Arg Val Val Pro Thr Glu Gly Ala Val
            1145                1150                1155
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gtg gaa gcg aag ttt cac act cgc atc ggg gcc agg gca ctg atg acg   40992
Val Glu Ala Lys Phe His Thr Arg Ile Gly Ala Arg Ala Leu Met Thr
       1160                1165                1170

ctg aaa cgg gaa gat ggt agc gcc att cct ttc ggg gcg cag gtt aca   41040
Leu Lys Arg Glu Asp Gly Ser Ala Ile Pro Phe Gly Ala Gln Val Thr
   1175                1180                1185

gtc aat ggg cag gat ggc agt gct gct ctg gtg gat act gat agc cag   41088
Val Asn Gly Gln Asp Gly Ser Ala Ala Leu Val Asp Thr Asp Ser Gln
1190                1195                1200                1205

gtt tat ctc act ggt ttg gcg gat aag ggc gaa ctg acg gtg aaa tgg   41136
Val Tyr Leu Thr Gly Leu Ala Asp Lys Gly Glu Leu Thr Val Lys Trp
                1210                1215                1220

gga gca cag caa tgt cgg gtt aac tac cgc cta cct gcc cac aag gga   41184
Gly Ala Gln Gln Cys Arg Val Asn Tyr Arg Leu Pro Ala His Lys Gly
            1225                1230                1235

atc gcg ggc ttg tat caa atg agc ggt ctc tgc aga tag ccgattctga   41233
Ile Ala Gly Leu Tyr Gln Met Ser Gly Leu Cys Arg
       1240                1245                1250

aggagagaat a atg tgg atg aaa ata cag cga gtg aaa acg gtt atc tat   41283
             Met Trp Met Lys Ile Gln Arg Val Lys Thr Val Ile Tyr
                        1255                1260

agc gta agc tta ctg gtc gct gcc agt agc ttg gtg ccg ata gcg aac   41331
Ser Val Ser Leu Leu Val Ala Ala Ser Ser Leu Val Pro Ile Ala Asn
   1265                1270                1275

gcc gca gaa aaa ctt cag aca acg cta cgt gta ggt act tac ttt cgg   41379
Ala Ala Glu Lys Leu Gln Thr Thr Leu Arg Val Gly Thr Tyr Phe Arg
1280                1285                1290                1295

gct ggg cac gtg cca gat ggg atg gtg ctt gcg caa ggc tgg gtg act   41427
Ala Gly His Val Pro Asp Gly Met Val Leu Ala Gln Gly Trp Val Thr
                1300                1305                1310

tat cac ggc agt cac agc ggg ttt cgg gta tgg agc gat gag caa aag   41475
Tyr His Gly Ser His Ser Gly Phe Arg Val Trp Ser Asp Glu Gln Lys
            1315                1320                1325

gcg ggt aac acg cct acc gta ttg ctg ctg agc ggg caa cag gat cct   41523
Ala Gly Asn Thr Pro Thr Val Leu Leu Leu Ser Gly Gln Gln Asp Pro
       1330                1335                1340

cgc cat cac att cag gtt cgc ctg gag ggc gag ggg tgg caa cca gat   41571
Arg His His Ile Gln Val Arg Leu Glu Gly Glu Gly Trp Gln Pro Asp
   1345                1350                1355

acg gtg agt ggt cgt ggc gcc att tta aga acc gct gca gat aac gcc   41619
Thr Val Ser Gly Arg Gly Ala Ile Leu Arg Thr Ala Ala Asp Asn Ala
1360                1365                1370                1375

agt ttc agt gtg gtc gtt gat ggc aat cag gaa gtg cct gcg gac acc   41667
Ser Phe Ser Val Val Val Asp Gly Asn Gln Glu Val Pro Ala Asp Thr
                1380                1385                1390

tgg acg ctg gat ttt aag gcc tgt gca ttg gcg cag gag gat acg tag   41715
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Trp Thr Leu Asp Phe Lys Ala Cys Ala Leu Ala Gln Glu Asp Thr
1395 1400 1405

ccgtctgttc cactcatact tcctgtatca gtgaataagg cgaatactgt atatcaggtt 41775

cgaggatgta ttgaaaattt actcaaggca aatatggtta gcaatcttca ttgcagaaaa 41835

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<213> Salmonella typhimurium

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Ala Ala Ser Cys Tyr Ala Gly Ser Phe Leu Pro Asn Ser Glu Gln Gln
            20                  25                  30
Lys Ser Val Asp Ile Val Phe Ser Ser Pro Gln Asp Leu Thr Val Ser
        35                  40                  45
Leu Ile Pro Val Ser Gly Leu Lys Ala Gly Lys Asn Ala Pro Ser Ala
    50                  55                  60
Lys Ile Ala Lys Leu Val Val Asn Ser Thr Thr Leu Lys Glu Phe Gly
65                  70                  75                  80
Val Arg Gly Ile Ser Asn Asn Val Val Asp Ser Thr Gly Thr Ala Trp
                85                  90                  95
Arg Val Ala Gly Lys Asn Thr Gly Lys Glu Ile Gly Val Gly Leu Ser
            100                 105                 110
Ser Asp Ser Leu Arg Arg Ser Asp Ser Thr Glu Lys Trp Asn Gly Val
        115                 120                 125
Asn Trp Met Thr Phe Asn Ser Asn Asp Thr Leu Asp Ile Val Leu Thr
    130                 135                 140
Gly Pro Ala Gln Asn Val Thr Ala Asp Thr Tyr Pro Ile Thr Leu Asp
145                 150                 155                 160
Val Val Gly Tyr Gln Pro
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<213> Salmonella typhimurium

<400> 3

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Met Lys Ile Val Asn Phe Ala Val Met Ala Val Ala Leu Phe Ala Thr
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Asn Ser Met Val Ser Val Tyr Ala Val Asn Gln Gln Leu Asn Ser Ala
            20                  25                  30
Thr Lys Leu Phe Ser Val Lys Leu Gly Ala Thr Arg Val Ile Tyr His
        35                  40                  45
Ala Gly Thr Ala Gly Ala Thr Leu Ser Val Ser Asn Pro Gln Asn Tyr
    50                  55                  60
Pro Ile Leu Val Gln Ser Ser Val Lys Ala Ala Asp Lys Ser Ser Pro
65                  70                  75                  80
Ala Pro Phe Leu Val Met Pro Pro Leu Phe Arg Leu Glu Ala Asn Gln
                85                  90                  95
Gln Ser Gln Leu Arg Ile Val Arg Thr Gly Gly Asp Met Pro Thr Asp
            100                 105                 110
Arg Glu Thr Leu Gln Trp Val Cys Ile Lys Ala Val Pro Pro Glu Asn
```

```
        115                 120                 125

Glu Pro Ser Asp Thr Gln Ala Lys Gly Ala Thr Leu Asp Leu Asn Leu
    130                 135                 140

Ser Ile Asn Ala Cys Asp Lys Leu Ile Phe Arg Pro Asp Ala Val Lys
145                 150                 155                 160

Gly Thr Pro Glu Asp Val Ala Gly Asn Leu Arg Trp Val Glu Thr Gly
                165                 170                 175

Asn Lys Leu Lys Val Glu Asn Pro Thr Pro Phe Tyr Met Asn Leu Ala
            180                 185                 190

Ser Val Thr Val Gly Gly Lys Pro Ile Thr Gly Leu Glu Tyr Val Pro
        195                 200                 205

Pro Phe Ala Asp Lys Thr Leu Asn Met Pro Gly Ser Ala His Gly Asp
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Ile Glu Trp Arg Val Ile Thr Asp Phe Gly Gly Glu Ser His Pro Phe
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His Tyr Val Leu Lys
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<212> PRT
<213> Salmonella typhimurium

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His Cys Ala Asn Ala His Thr Tyr Thr Phe Asp Ala Ser Met Leu Gly
            20                  25                  30

Asp Ala Ala Lys Gly Val Asp Met Ser Leu Phe Asn Gln Gly Leu Gln
        35                  40                  45

Gln Pro Gly Thr Tyr Arg Val Asp Val Met Val Asn Gly Lys Arg Val
    50                  55                  60

Asp Thr Arg Asp Val Val Phe Lys Leu Glu Lys Asp Gly Gln Gly Thr
65                  70                  75                  80

Pro Val Leu Ala Pro Cys Leu Thr Val Ser Gln Leu Ser Arg Tyr Gly
                85                  90                  95

Val Lys Thr Glu Asp Tyr Pro Gln Leu Trp Lys Ala Ala Lys Pro Pro
            100                 105                 110

Asp Glu Cys Ala Asp Leu Thr Ala Ile Pro Gln Ala Lys Ala Val Leu
        115                 120                 125

Asp Ile Asn Asn Gln Gln Leu Gln Leu Ser Ile Pro Gln Leu Ala Leu
    130                 135                 140

Arg Pro Glu Phe Lys Gly Ile Ala Pro Glu Asp Leu Trp Asp Asp Gly
```

```
145                 150                 155                 160

Ile Pro Ala Phe Leu Met Asn Tyr Ser Ala Arg Thr Thr Gln Thr Asp
                165                 170                 175

Tyr Lys Met Asp Met Val Gly Arg Asp Asn Ser Ser Trp Val Gln Leu
            180                 185                 190

Gln Pro Gly Ile Asn Ile Gly Ala Trp Arg Val Arg Asn Ala Thr Ser
        195                 200                 205

Trp Gln Arg Ser Ser Gln Leu Ser Gly Lys Trp Gln Ala Ala Tyr Thr
    210                 215                 220

Tyr Ala Glu Arg Gly Leu Tyr Ser Leu Lys Ser Arg Leu Thr Leu Gly
225                 230                 235                 240

Gln Lys Thr Ser Gln Gly Glu Ile Phe Asp Ser Val Pro Phe Thr Gly
                245                 250                 255

Val Met Leu Ala Ser Asp Asp Asn Met Val Pro Tyr Ser Glu Arg Gln
            260                 265                 270

Phe Ala Pro Val Val Arg Gly Ile Ala Arg Thr Gln Ala Arg Val Glu
        275                 280                 285

Val Lys Gln Asn Gly Tyr Thr Ile Tyr Asn Thr Thr Val Ala Pro Gly
    290                 295                 300

Pro Phe Ala Leu Arg Asp Leu Ser Val Thr Asp Ser Ser Gly Asp Leu
305                 310                 315                 320

His Val Thr Val Trp Glu Ala Asp Gly Ser Thr Gln Met Phe Val Val
                325                 330                 335

Pro Tyr Gln Thr Pro Ala Ile Ala Leu His Gln Gly Tyr Leu Lys Tyr
            340                 345                 350

Ser Leu Leu Ala Gly Arg Tyr Arg Ser Ser Asp Ser Ala Thr Asp Lys
        355                 360                 365

Arg Gln Ile Ala Gln Ala Thr Leu Met Tyr Gly Leu Pro Trp Asn Leu
    370                 375                 380

Thr Ala Tyr Gly Gly Ile Gln Ser Ala Thr His Asn Gln Ala Ala Leu
385                 390                 395                 400

Leu Gly Leu Gly Gly Ser Leu Gly Arg Trp Gly Ser Leu Ser Val Asp
                405                 410                 415

Gly Ser Asp Thr His Ser Gln Arg Gln Gly Glu Ala Val Gln Gln Gly
            420                 425                 430

Ala Ser Trp Arg Leu Arg Tyr Ser Asn Gln Leu Thr Ala Thr Gly Thr
        435                 440                 445

Asn Phe Phe Leu Thr Arg Trp Gln Tyr Ala Ser Gln Gly Tyr Asn Thr
    450                 455                 460

Leu Ser Asp Val Leu Asp Ser Tyr Arg His Asn Gly Asn Arg Leu Trp
465                 470                 475                 480
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Ser Trp Arg Glu Asn Leu Gln Pro Ser Ser Arg Thr Thr Leu Met Leu
                485                 490                 495

Ser Gln Ser Trp Gly Arg His Leu Gly Asn Leu Ser Leu Thr Gly Ser
            500                 505                 510

Arg Thr Asp Trp Arg Asn Arg Pro Gly His Asp Asp Ser Tyr Gly Leu
        515                 520                 525

Ser Trp Gly Thr Ser Ile Gly Gly Gly Ser Leu Ser Leu Asn Trp Asn
    530                 535                 540

Gln Asn Arg Thr Leu Trp Arg Asn Gly Ala His Arg Lys Glu Asn Ile
545                 550                 555                 560

Thr Ser Leu Trp Phe Ser Met Pro Leu Ser Arg Trp Thr Gly Asn Asn
                565                 570                 575

Val Ser Ala Ser Trp Gln Met Thr Ser Pro Ser His Gly Gly Gln Thr
            580                 585                 590

Gln Gln Val Gly Val Asn Gly Glu Ala Phe Ser Gln Gln Leu Asp Trp
        595                 600                 605

Glu Val Arg Gln Ser Tyr Arg Ala Asp Ala Pro Pro Gly Gly Gly Asn
    610                 615                 620

Asn Ser Ala Leu His Leu Ala Trp Asn Gly Asp Tyr Gly Leu Leu Gly
625                 630                 635                 640

Gly Asp Tyr Ser Tyr Ser Arg Ala Met Arg Gln Met Gly Val Asn Ile
                645                 650                 655

Ala Gly Gly Ile Val Ile His His His Gly Val Thr Leu Gly Gln Pro
            660                 665                 670

Leu Gln Gly Ser Val Ala Leu Val Glu Ala Pro Gly Ala Ser Gly Val
        675                 680                 685

Pro Val Gly Gly Trp Pro Gly Val Lys Thr Asp Phe Arg Gly Asp Thr
    690                 695                 700

Thr Val Gly Asn Leu Asn Val Tyr Gln Glu Asn Thr Val Ser Leu Asp
705                 710                 715                 720

Pro Ser Arg Leu Pro Asp Asp Ala Glu Val Thr Gln Thr Asp Val Arg
                725                 730                 735

Val Val Pro Thr Glu Gly Ala Val Val Glu Ala Lys Phe His Thr Arg
            740                 745                 750

Ile Gly Ala Arg Ala Leu Met Thr Leu Lys Arg Glu Asp Gly Ser Ala
        755                 760                 765

Ile Pro Phe Gly Ala Gln Val Thr Val Asn Gly Gln Asp Gly Ser Ala
    770                 775                 780

Ala Leu Val Asp Thr Asp Ser Gln Val Tyr Leu Thr Gly Leu Ala Asp
785                 790                 795                 800
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Lys Gly Glu Leu Thr Val Lys Trp Gly Ala Gln Gln Cys Arg Val Asn
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Tyr Arg Leu Pro Ala His Lys Gly Ile Ala Gly Leu Tyr Gln Met Ser
            820                 825                 830

Gly Leu Cys Arg
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<210> 5
<211> 156
<212> PRT
<213> Salmonella typhimurium

<400> 5

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Leu Leu Val Ala Ala Ser Ser Leu Val Pro Ile Ala Asn Ala Ala Glu
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Lys Leu Gln Thr Thr Leu Arg Val Gly Thr Tyr Phe Arg Ala Gly His
        35                  40                  45

Val Pro Asp Gly Met Val Leu Ala Gln Gly Trp Val Thr Tyr His Gly
    50                  55                  60

Ser His Ser Gly Phe Arg Val Trp Ser Asp Glu Gln Lys Ala Gly Asn
65                  70                  75                  80

Thr Pro Thr Val Leu Leu Leu Ser Gly Gln Gln Asp Pro Arg His His
                85                  90                  95

Ile Gln Val Arg Leu Glu Gly Glu Gly Trp Gln Pro Asp Thr Val Ser
            100                 105                 110

Gly Arg Gly Ala Ile Leu Arg Thr Ala Ala Asp Asn Ala Ser Phe Ser
        115                 120                 125

Val Val Val Asp Gly Asn Gln Glu Val Pro Ala Asp Thr Trp Thr Leu
    130                 135                 140

Asp Phe Lys Ala Cys Ala Leu Ala Gln Glu Asp Thr
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SEQUENCE LISTING NO. 2

<110> Folkesson, Anders

<120> The complete sequence of the tcf insert of Salmonella enterica serovar Typhi.

<130> The tcf insert in Salmonella typhi

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<170> PatentIn Ver. 2.1

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ctaaaattta gatgactttt atacggtaaa atctggt atg aat ttt aaa gat act 1915
Met Asn Phe Lys Asp Thr
1 5

ctt ccc ggg gtg ttt ctc tgt gtc gct atg ttt gca tgt ggt cat gcc 1963
Leu Pro Gly Val Phe Leu Cys Val Ala Met Phe Ala Cys Gly His Ala
10 15 20

agg gcg aat atg ctc gtt tat ccc atg gcg gca gaa att aat agt agc 2011
Arg Ala Asn Met Leu Val Tyr Pro Met Ala Ala Glu Ile Asn Ser Ser
25 30 35

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cgc gaa gag gcc acc tcg ctg ttc gtc tat tct aaa tca gat cat gtg   2059
Arg Glu Glu Ala Thr Ser Leu Phe Val Tyr Ser Lys Ser Asp His Val
     40                  45                  50

caa tat att cga aca aga atc atg cgt att gaa cac ccc ggt atg cca   2107
Gln Tyr Ile Arg Thr Arg Ile Met Arg Ile Glu His Pro Gly Met Pro
 55                  60                  65                  70

cag gag aag gag gta cca gca ggg aat gat ata gag aca gga ctt gtt   2155
Gln Glu Lys Glu Val Pro Ala Gly Asn Asp Ile Glu Thr Gly Leu Val
                 75                  80                  85

gtc tcc ccg gag aaa ttt gct ctt tcc ccg gga aca aaa aaa aca ata   2203
Val Ser Pro Glu Lys Phe Ala Leu Ser Pro Gly Thr Lys Lys Thr Ile
            90                  95                 100

cgt gtt atc agt act cag gca ccg gaa aga gag gaa gcc tgg cgg gta   2251
Arg Val Ile Ser Thr Gln Ala Pro Glu Arg Glu Glu Ala Trp Arg Val
        105                 110                 115

tac ttc gag gct gtt cct gaa ctg gaa gat gat cca cag gca ggc gga   2299
Tyr Phe Glu Ala Val Pro Glu Leu Glu Asp Asp Pro Gln Ala Gly Gly
    120                 125                 130

aag caa aat tca tcc gta agt gtg aat ctt gtc tgg ggg gtg ttg ctg   2347
Lys Gln Asn Ser Ser Val Ser Val Asn Leu Val Trp Gly Val Leu Leu
135                 140                 145                 150

cgt gtt tct ccg tca gac ccc agg cct gcg ctg gta acg gac ggt cac   2395
Arg Val Ser Pro Ser Asp Pro Arg Pro Ala Leu Val Thr Asp Gly His
                155                 160                 165

cac ctg ctg aat acg gga aac aca cgg ctt tct ctt att cgg gct ggc   2443
His Leu Leu Asn Thr Gly Asn Thr Arg Leu Ser Leu Ile Arg Ala Gly
            170                 175                 180

aac tgc gac acc aca tgc cac tgg cag aat ata ggc aaa agt att tat   2491
Asn Cys Asp Thr Thr Cys His Trp Gln Asn Ile Gly Lys Ser Ile Tyr
        185                 190                 195

ccc ggc ggg agt gct gat att ccg gcc gga ata aaa agt aat gca ttt   2539
Pro Gly Gly Ser Ala Asp Ile Pro Ala Gly Ile Lys Ser Asn Ala Phe
    200                 205                 210

cgt gtg gaa tat cgt acg ggt gca aat tca ccg gta atc tct gct gat   2587
Arg Val Glu Tyr Arg Thr Gly Ala Asn Ser Pro Val Ile Ser Ala Asp
215                 220                 225                 230

tta aca gca gcc gga aag taa aaacacacgg agcgtacgct ataccctaca      2638
Leu Thr Ala Ala Gly Lys
                235

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                      Met Tyr Thr Glu Cys Thr Tyr Ile Thr Val Ile
                           240                 245

aac aac aaa gca agg tta ttt ttt atg aac atg aaa aca tct ttt att   2739
Asn Asn Lys Ala Arg Leu Phe Phe Met Asn Met Lys Thr Ser Phe Ile
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    250                 255                 260

gcc gca gct gtg gca ttg gcc acc gtt tat tct ttt tct gtt tct gcg   2787
Ala Ala Ala Val Ala Leu Ala Thr Val Tyr Ser Phe Ser Val Ser Ala
265                 270                 275                 280

gtt cag aag gat att acc gtc act gcc aat att gac agt aca ctt gaa   2835
Val Gln Lys Asp Ile Thr Val Thr Ala Asn Ile Asp Ser Thr Leu Glu
                285                 290                 295

ctg ctg cag gcc gat ggt tca tcc ctc ccg tcg act atg aag ctg gat   2883
Leu Leu Gln Ala Asp Gly Ser Ser Leu Pro Ser Thr Met Lys Leu Asp
            300                 305                 310

ttc atg ccg ggt aag ggc ctg gtc cat aaa tca ctc cag acc cgc ctt   2931
Phe Met Pro Gly Lys Gly Leu Val His Lys Ser Leu Gln Thr Arg Leu
        315                 320                 325

tac agc aac gat cag acc aag tcg gtt aat gta aaa ctg ttg aat gct   2979
Tyr Ser Asn Asp Gln Thr Lys Ser Val Asn Val Lys Leu Leu Asn Ala
    330                 335                 340

cca caa ctt atc aac gtc ctg gat ccc acc aaa acc att gat atg gaa   3027
Pro Gln Leu Ile Asn Val Leu Asp Pro Thr Lys Thr Ile Asp Met Glu
345                 350                 355                 360

gtg act ctg gga gga cgg tca ctg acc acc acc aat tct gta ctg gaa   3075
Val Thr Leu Gly Gly Arg Ser Leu Thr Thr Thr Asn Ser Val Leu Glu
                365                 370                 375

gct aaa acc ctg ttc ccg gac gga aaa act ggc gat gct tca gct ctg   3123
Ala Lys Thr Leu Phe Pro Asp Gly Lys Thr Gly Asp Ala Ser Ala Leu
            380                 385                 390

ctg aac ctg gat att ggt cag aag gct gga gca gcc tta caa aac ctg   3171
Leu Asn Leu Asp Ile Gly Gln Lys Ala Gly Ala Ala Leu Gln Asn Leu
        395                 400                 405

cct gcc ggt gaa tac agc gga ttg gtc agt ctg gtg att tca cag gct   3219
Pro Ala Gly Glu Tyr Ser Gly Leu Val Ser Leu Val Ile Ser Gln Ala
    410                 415                 420

gtc act gcc ggc taa taactggtta ttagctcttc atctgatccg gttttggggg   3274
Val Thr Ala Gly
425

gcaccgttcg tacctgaacc ggatccggta ttgatcttat tattcattgc aattcaggtc 3334

tctttacgtg agtcgttatt tctgg atg tat tat tta ctg gga ttg tgc agt   3386
                          Met Tyr Tyr Leu Leu Gly Leu Cys Ser
                          430                 435

ttt acc agc cag gca act ctt att ccc cct cct gga ttt gaa tct ctg   3434
Phe Thr Ser Gln Ala Thr Leu Ile Pro Pro Pro Gly Phe Glu Ser Leu
    440                 445                 450

ctg gaa gga cag act gag caa att gaa gtg ttg cta cca ggg cat tca   3482
L u Glu Gly Gln Thr Glu Gln Ile Glu Val Leu Leu Pro Gly His Ser
455                 460                 465                 470
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ctg gga tta ttt ccg gtg gtg gtt aaa ccg gac acc gtg cag ttc atg   3530
Leu Gly Leu Phe Pro Val Val Val Lys Pro Asp Thr Val Gln Phe Met
                475                 480                 485

tcc cca ttg atg gta ctt gaa agc agt ggg ctt gcc gcg ttg ccg gcc   3578
Ser Pro Leu Met Val Leu Glu Ser Ser Gly Leu Ala Ala Leu Pro Ala
            490                 495                 500

gca gaa cgg caa aaa gcg ctg gct gca ctc agc cgt ccg ttg cta cgt   3626
Ala Glu Arg Gln Lys Ala Leu Ala Ala Leu Ser Arg Pro Leu Leu Arg
        505                 510                 515

aac agc aat ctg gtc tgt ggt gtc tca gaa gca aaa gac agc agc gag   3674
Asn Ser Asn Leu Val Cys Gly Val Ser Glu Ala Lys Asp Ser Ser Glu
    520                 525                 530

tgt ggt tac gtg gca aca gat aaa gag gat gtt gcg gtt att ttt gat   3722
Cys Gly Tyr Val Ala Thr Asp Lys Glu Asp Val Ala Val Ile Phe Asp
535                 540                 545                 550

gag aac aac gct cag tta tct ttg ttt ctt aac cgg gac tgg ttg ccg   3770
Glu Asn Asn Ala Gln Leu Ser Leu Phe Leu Asn Arg Asp Trp Leu Pro
                555                 560                 565

gat gaa gaa cga cgt gat aaa cgc tgg ctg act ccg acc ccg gag ggt   3818
Asp Glu Glu Arg Arg Asp Lys Arg Trp Leu Thr Pro Thr Pro Glu Gly
            570                 575                 580

gtc agc gca ttt att cac cgc cag acg ctg tat ctg agt gat gat ctc   3866
Val Ser Ala Phe Ile His Arg Gln Thr Leu Tyr Leu Ser Asp Asp Leu
        585                 590                 595

cac agt cgt aat atg aca ctg aat ggt agc ggt gcc ctg ggg ctt ggt   3914
His Ser Arg Asn Met Thr Leu Asn Gly Ser Gly Ala Leu Gly Leu Gly
    600                 605                 610

gac ggt cgt tat ctg gga ggc gac tgg gcg gct atc tgg aat cag tca   3962
Asp Gly Arg Tyr Leu Gly Gly Asp Trp Ala Ala Ile Trp Asn Gln Ser
615                 620                 625                 630

gaa cat tac aat aac agt cag gcc tgg ttt gac aat ctg ttt gtc cgt   4010
Glu His Tyr Asn Asn Ser Gln Ala Trp Phe Asp Asn Leu Phe Val Arg
                635                 640                 645

cag gat ctc ggc aat cag tat tat ctc cag gct ggt cgg atg gat cag   4058
Gln Asp Leu Gly Asn Gln Tyr Tyr Leu Gln Ala Gly Arg Met Asp Gln
            650                 655                 660

cgg aat ctg tcc agc gcc acg ggg ggg gat ttt ggg ttc agt ctg ctt   4106
Arg Asn Leu Ser Ser Ala Thr Gly Gly Asp Phe Gly Phe Ser Leu Leu
        665                 670                 675

ccc ctg agc cgg ttt gat gga tta cga acc ggg acc acc caa gct tat   4154
Pro Leu Ser Arg Phe Asp Gly Leu Arg Thr Gly Thr Thr Gln Ala Tyr
    680                 685                 690

gtt aac cat gag gtg gac cat aat gcc act ccg gtt atg gtt cag gtt   4202
Val Asn His Glu Val Asp His Asn Ala Thr Pro Val Met Val Gln Val
695                 700                 705                 710
```

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acc cga aat gcc cgt att gat att tat cgt ggc agc gag ttg ctg ggg    4250
Thr Arg Asn Ala Arg Ile Asp Ile Tyr Arg Gly Ser Glu Leu Leu Gly
                715                 720                 725

agt cag ttc ctg acc ccg gga atg cat acc ctg gat act cat tct ctt    4298
Ser Gln Phe Leu Thr Pro Gly Met His Thr Leu Asp Thr His Ser Leu
            730                 735                 740

cca ccg gga agc tat cct ctg gcg ttg cgg gtg tat gag gat ggg att    4346
Pro Pro Gly Ser Tyr Pro Leu Ala Leu Arg Val Tyr Glu Asp Gly Ile
        745                 750                 755

ctg cgg cga acg gag acc cag ccc ttc agt aag ggg ggc aat agc ttc    4394
Leu Arg Arg Thr Glu Thr Gln Pro Phe Ser Lys Gly Gly Asn Ser Phe
    760                 765                 770

agt gca cag acc cag tgg ttt att cag ggc ggg ctg gaa gat acc ggg    4442
Ser Ala Gln Thr Gln Trp Phe Ile Gln Gly Gly Leu Glu Asp Thr Gly
775                 780                 785                 790

gat aaa gcc agc cat tat gac ggt gag act gtc atg gct gcc gga ttc    4490
Asp Lys Ala Ser His Tyr Asp Gly Glu Thr Val Met Ala Ala Gly Phe
                795                 800                 805

caa act ggg ctg cgg aaa aat atc agt ctg acc gaa ggt atc tct ctg    4538
Gln Thr Gly Leu Arg Lys Asn Ile Ser Leu Thr Glu Gly Ile Ser Leu
            810                 815                 820

gca cat gag gcc tgg tac agt gaa acc cga ctg aat tca cag cat gca    4586
Ala His Glu Ala Trp Tyr Ser Glu Thr Arg Leu Asn Ser Gln His Ala
        825                 830                 835

gtg ctg gat ggc acg ctg gac ctt tct gcc ggg ata ctg cat ggg aca    4634
Val Leu Asp Gly Thr Leu Asp Leu Ser Ala Gly Ile Leu His Gly Thr
    840                 845                 850

gac agc acg agc ggt aac act gag cag gtg aca tac aac gac gga ttt    4682
Asp Ser Thr Ser Gly Asn Thr Glu Gln Val Thr Tyr Asn Asp Gly Phe
855                 860                 865                 870

tcc gcg agt ctg tgg cgt aac cat acg gaa agt gat gcc tgt agt ggt    4730
Ser Ala Ser Leu Trp Arg Asn His Thr Glu Ser Asp Ala Cys Ser Gly
                875                 880                 885

cgt cat cca cag tca gtg cat gcc agt atg acc tgc cag act tcg atg    4778
Arg His Pro Gln Ser Val His Ala Ser Met Thr Cys Gln Thr Ser Met
            890                 895                 900

aac gcc tcc ctg tcg gtt tcg gtg ggg aac tgg tat gcc cta ctg gga    4826
Asn Ala Ser Leu Ser Val Ser Val Gly Asn Trp Tyr Ala Leu Leu Gly
        905                 910                 915

tac agt acc agc agg aca gaa ggt cgg ccg gtt tac cgg gga tat gat    4874
Tyr Ser Thr Ser Arg Thr Glu Gly Arg Pro Val Tyr Arg Gly Tyr Asp
    920                 925                 930

gat aac agt gac aaa gaa aat gtg ttc tgg cga cag gca tac atc cct    4922
Asp Asn Ser Asp Lys Glu Asn Val Phe Trp Arg Gln Ala Tyr Ile Pro
935                 940                 945                 950
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gcc tct cac cgc gaa tct gct cag gct agt gca acg tac agc ctt aat   4970
Ala Ser His Arg Glu Ser Ala Gln Ala Ser Ala Thr Tyr Ser Leu Asn
                955                 960                 965

atg gct ggc atg aat att aat acc cat ggg gga gta tgg cga acc cga   5018
Met Ala Gly Met Asn Ile Asn Thr His Gly Gly Val Trp Arg Thr Arg
            970                 975                 980

aat gac gga gtg aat gat gat ggc ttg ttt atg agt gtc agt gtg tca   5066
Asn Asp Gly Val Asn Asp Asp Gly Leu Phe Met Ser Val Ser Val Ser
        985                 990                 995

tat gcc tct caa cca ccg aca atg act ggc agt aat agg tat acc tca   5114
Tyr Ala Ser Gln Pro Pro Thr Met Thr Gly Ser Asn Arg Tyr Thr Ser
   1000                1005                1010

gcc ggg acc gat att cac agt agc cgg aat caa aaa aca cag acg tcc   5162
Ala Gly Thr Asp Ile His Ser Ser Arg Asn Gln Lys Thr Gln Thr Ser
1015                1020                1025                1030

tgg aat gtg aac cat gtg aga tcc tgg cag cag gat ctg tat cgt gaa   5210
Trp Asn Val Asn His Val Arg Ser Trp Gln Gln Asp Leu Tyr Arg Glu
                1035                1040                1045

ctg tcg gtg ggt ttc tcc ggt tat aac gac gac agc tgg agc ggg agt   5258
Leu Ser Val Gly Phe Ser Gly Tyr Asn Asp Asp Ser Trp Ser Gly Ser
            1050                1055                1060

ctc ggc gga cgc atg agc ggc cgt atg ggt gaa ctg agc gcc act atc   5306
Leu Gly Gly Arg Met Ser Gly Arg Met Gly Glu Leu Ser Ala Thr Ile
        1065                1070                1075

agt aac tcc cat caa cgt aat gcg ggc agc gcc agt tca ctc acc gct   5354
Ser Asn Ser His Gln Arg Asn Ala Gly Ser Ala Ser Ser Leu Thr Ala
   1080                1085                1090

ggc tac agc tcg tct ctg gcg tta tcc cgt aat gga ctg ttc tgg gga   5402
Gly Tyr Ser Ser Ser Leu Ala Leu Ser Arg Asn Gly Leu Phe Trp Gly
1095                1100                1105                1110

ggt ggt cag gac ggt gaa ccg gcc tct ggc atg gcg gtg aac gtg gag   5450
Gly Gly Gln Asp Gly Glu Pro Ala Ser Gly Met Ala Val Asn Val Glu
                1115                1120                1125

tca gag ggg gac gag ggc agt agc ggg aaa gta gtc agc gtt cgt ggc   5498
Ser Glu Gly Asp Glu Gly Ser Ser Gly Lys Val Val Ser Val Arg Gly
            1130                1135                1140

agc agc cag ccg ttc agt ctc ggt ttt ggt cag cag tcg ctg ttg ctg   5546
Ser Ser Gln Pro Phe Ser Leu Gly Phe Gly Gln Gln Ser Leu Leu Leu
        1145                1150                1155

atg gaa ggc tat aac gcc acg gag gtg acc att gag gat gca ggg gtt   5594
Met Glu Gly Tyr Asn Ala Thr Glu Val Thr Ile Glu Asp Ala Gly Val
   1160                1165                1170

agt tca cag ggt atg gca ggc gta aaa gcg gga ggg gga agc agg tgt   5642
Ser Ser Gln Gly Met Ala Gly Val Lys Ala Gly Gly Gly Ser Arg Cys
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1175                1180                1185                1190

tac ttc ctg aca ccc ggg cat ctg ctg gtt cac aac atc agc gcc agt   5690
Tyr Phe Leu Thr Pro Gly His Leu Leu Val His Asn Ile Ser Ala Ser
                1195                1200                1205

atg agc cga ctg tac gtt ggc cgc gta ctg gac aag gat ggc aga ccg   5738
Met Ser Arg Leu Tyr Val Gly Arg Val Leu Asp Lys Asp Gly Arg Pro
            1210                1215                1220

ctg ctg gac gca cag cca ctg aac tat cca ttt ttg tcg ttg gga cct   5786
Leu Leu Asp Ala Gln Pro Leu Asn Tyr Pro Phe Leu Ser Leu Gly Pro
        1225                1230                1235

tcc ggg cga ttt agc ctg cag agc gag cat aaa gaa tcc agc ctg tgg   5834
Ser Gly Arg Phe Ser Leu Gln Ser Glu His Lys Glu Ser Ser Leu Trp
    1240                1245                1250

ctg ctg tct aaa aac agg atc ctg cgt tgt ccg atg tca gta cat aaa   5882
Leu Leu Ser Lys Asn Arg Ile Leu Arg Cys Pro Met Ser Val His Lys
1255                1260                1265                1270

cgt cgg gat gtt atg cag gta gtg ggt gat gtg cgg tgt gaa tta agt   5930
Arg Arg Asp Val Met Gln Val Val Gly Asp Val Arg Cys Glu Leu Ser
                1275                1280                1285

gac gtg gat gcc ctg cca cag gcg ttg caa ata tcg ccg cgg gtc atc   5978
Asp Val Asp Ala Leu Pro Gln Ala Leu Gln Ile Ser Pro Arg Val Ile
            1290                1295                1300

cgt ttg ctg aac gtg gca ggt ttg ctg cgc cat tcc gtt cag gaa gcc   6026
Arg Leu Leu Asn Val Ala Gly Leu Leu Arg His Ser Val Gln Glu Ala
        1305                1310                1315

tga cgtagagata aaggcgttaa ct atg agt aat aaa atg aag tgg acg agt   6078
                            Met Ser Asn Lys Met Lys Trp Thr Ser
                        1320                1325

atg aca gcc cat tgg tca gca att att aat ttc atc cga aaa tat gtt   6126
Met Thr Ala His Trp Ser Ala Ile Ile Asn Phe Ile Arg Lys Tyr Val
    1330                1335                1340

tat cca gca agg ata att gcc atc ctg ctg atg gct ggc gct aca ctg   6174
Tyr Pro Ala Arg Ile Ile Ala Ile Leu Leu Met Ala Gly Ala Thr Leu
1345                1350                1355                1360

cca caa gtc gcc gat gcg att acc gtc gac ctg aat tac gac aag aac   6222
Pro Gln Val Ala Asp Ala Ile Thr Val Asp Leu Asn Tyr Asp Lys Asn
                1365                1370                1375

aat gta gcg gtc atc act cct gtc tgg tcc caa gaa tgg agt gta gca   6270
Asn Val Ala Val Ile Thr Pro Val Trp Ser Gln Glu Trp Ser Val Ala
            1380                1385                1390

aat gtg ttg ggg gga tgg gta tgt cgt tca aac agg aat gaa aat gag   6318
Asn Val Leu Gly Gly Trp Val Cys Arg Ser Asn Arg Asn Glu Asn Glu
        1395                1400                1405

ggg gcg tgt gaa gaa aca cat ttg gta tgg tgg tat gct ttt gga gct   6366
Gly Ala Cys Glu Glu Thr His Leu Val Trp Trp Tyr Ala Phe Gly Ala
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   1410                1415                1420

tat tca aaa att cgt ctg cgt ttc aga gaa caa atc agc cat gcc gaa   6414
Tyr Ser Lys Ile Arg Leu Arg Phe Arg Glu Gln Ile Ser His Ala Glu
1425                1430                1435                1440

att acg ctc ata ctg ctc ggc agt gtt cgt gat gcc tgt tat act ggt   6462
Ile Thr Leu Ile Leu Leu Gly Ser Val Arg Asp Ala Cys Tyr Thr Gly
                1445                1450                1455

gtc atc aac atg aac gct gct gca tgt caa tgg ggt agg tcg ctg aaa   6510
Val Ile Asn Met Asn Ala Ala Ala Cys Gln Trp Gly Arg Ser Leu Lys
            1460                1465                1470

ctt agg ata cct tca gaa gag ctt gcg aag ata cct aca agc gga aca   6558
Leu Arg Ile Pro Ser Glu Glu Leu Ala Lys Ile Pro Thr Ser Gly Thr
        1475                1480                1485

tgg aaa gca acg tta gtc ctg gat tat tta caa tgg ggc gga gac gat   6606
Trp Lys Ala Thr Leu Val Leu Asp Tyr Leu Gln Trp Gly Gly Asp Asp
    1490                1495                1500



cct tta ggc aca tca act aca gat atc acg ctg aat gta aca gac cac   6654
Pro Leu Gly Thr Ser Thr Thr Asp Ile Thr Leu Asn Val Thr Asp His
1505                1510                1515                1520

ttt gct gaa aat gcg gct att tac ttt ccg caa ttt ggt aca gca acg   6702
Phe Ala Glu Asn Ala Ala Ile Tyr Phe Pro Gln Phe Gly Thr Ala Thr
                1525                1530                1535

ccc cgg gtg gac ctg aat ctt cac cgg atg aat gcc tca caa atg tcg   6750
Pro Arg Val Asp Leu Asn Leu His Arg Met Asn Ala Ser Gln Met Ser
            1540                1545                1550

ggc agg gct aat ctg gat atg tgt ctg tat gac gga ggt gtg aaa gcc   6798
Gly Arg Ala Asn Leu Asp Met Cys Leu Tyr Asp Gly Gly Val Lys Ala
        1555                1560                1565

cgt tca tta cag atg aag ata gaa gga agc aat aag tca ggt acg gga   6846
Arg Ser Leu Gln Met Lys Ile Glu Gly Ser Asn Lys Ser Gly Thr Gly
    1570                1575                1580

ttt cag gtt ata aag agc gat tct gct gat acg att gat tat gcg gtc   6894
Phe Gln Val Ile Lys Ser Asp Ser Ala Asp Thr Ile Asp Tyr Ala Val
1585                1590                1595                1600

agt atg aat tat ggg gga cga agt att cct gtc acc cgt ggc gtg gag   6942
Ser Met Asn Tyr Gly Gly Arg Ser Ile Pro Val Thr Arg Gly Val Glu
                1605                1610                1615

ttc agt ctg gat aac gtg gat aaa gca gca acg cgt ccg gtg gta ctt   6990
Phe Ser Leu Asp Asn Val Asp Lys Ala Ala Thr Arg Pro Val Val Leu
            1620                1625                1630

ccc ggg caa cgg cag gcg gta cgt tgt gtg cca gtg ccc ctt acc ctg   7038
Pro Gly Gln Arg Gln Ala Val Arg Cys Val Pro Val Pro Leu Thr Leu
        1635                1640                1645
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aca aca caa ccc ttt aac atc aga gag aag cgt tct ggt gag tat cag   7086
Thr Thr Gln Pro Phe Asn Ile Arg Glu Lys Arg Ser Gly Glu Tyr Gln
   1650                1655                1660

gga acg ctg aca gtg aca atg ctg atg gga aca caa acc ccc tga       7131
Gly Thr Leu Thr Val Thr Met Leu Met Gly Thr Gln Thr Pro
1665               1670                1675

cagtaattat ttattttatt gatatctttc ttatatggtt ttttaaatca gagttctctt 7191

tatatacttg ttttatttaa taaagagaat ctattcactt atgaaaatca atgcgtgagg 7251

ttctgctttc ct atg act gtg tat tta gat gat aaa gat aaa gaa tta ttg 7302
             Met Thr Val Tyr Leu Asp Asp Lys Asp Lys Glu Leu Leu
            1680                1685                1690

aaa gaa atc caa aaa gat tgt gca caa act tta tgg caa ctt gca tat   7350
Lys Glu Ile Gln Lys Asp Cys Ala Gln Thr Leu Trp Gln Leu Ala Tyr
       1695                1700                1705

aaa gtg gga ctt acg ccc aca cca tgt ttc aaa cgt tta aaa aaa ctt   7398
Lys Val Gly Leu Thr Pro Thr Pro Cys Phe Lys Arg Leu Lys Lys Leu
   1710                1715                1720

aaa gac agg ggg gtt atc att ggt cag ttc gct tta ttg gat aag gaa   7446
Lys Asp Arg Gly Val Ile Ile Gly Gln Phe Ala Leu Leu Asp Lys Glu
1725               1730                1735                1740

aaa cta ggt ctt tca ctt aat gtc ttt att atg att aac ata tct gag   7494
Lys Leu Gly Leu Ser Leu Asn Val Phe Ile Met Ile Asn Ile Ser Glu
                1745                1750                1755

gag caa tac gct agt att tct gag aaa ata aag tca atg cct gag gtt   7542
Glu Gln Tyr Ala Ser Ile Ser Glu Lys Ile Lys Ser Met Pro Glu Val
           1760                1765                1770

att gcc ttt tat cga att tct gga tca ttt aat tat tta atg cat aca   7590
Ile Ala Phe Tyr Arg Ile Ser Gly Ser Phe Asn Tyr Leu Met His Thr
       1775                1780                1785

gta ttt aca gat atg aac gat tac tat agt ttt tat gag aaa ata ata   7638
Val Phe Thr Asp Met Asn Asp Tyr Tyr Ser Phe Tyr Glu Lys Ile Ile
   1790                1795                1800

tta act aat tct tca att agt gga tct gca tcg agc ttt gtt ctt gag   7686
Leu Thr Asn Ser Ser Ile Ser Gly Ser Ala Ser Ser Phe Val Leu Glu
1805               1810                1815                1820

caa ata aag gaa aca aac gaa ctg tca gtg tga aagtgtgatg tgtacttact 7739
Gln Ile Lys Glu Thr Asn Glu Leu Ser Val
               1825                1830

gatttaatac attattatcc ttcttacgga acaacaacgg cagattgcgg ctgttgaaca 7799

aggattttaa tcagcagtgg tgaaattaag cggcacagaa taacacagcg gaatatcaca 7859

tggttaaata tcaccccgtg catgtaacaa aaaaccgcat taaaacagat gatgttactg 7919

atatttattt cgttgaaccc ttctggaaaa aaggcgaaaa ccacataatt gagtcattga 7979
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tgtttttga agagttacaa aagtcattta atttattcaa ccataaatat gggttaaata 8039

aatatatact caggatcccc tgggaatttg tgctcataca tatggaaagg atcagtaaat 8099

taaatagcgt cgggttattt gctgtttctg ttgactttaa taacaaccac aaatttctga 8159

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tcatgctgaa ggcggtttca gatctggagg cattgggtta tttatgacgg gaacaagaga 8999

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cctccacgtc ctgaagggcg tgggttcctg ctccaacggg ctgcctgact gcacgctcct 9119

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<211> 236
<212> PRT
<213> Salmonella typhi

<400> 2

Met	Asn	Phe	Lys	Asp	Thr	Leu	Pro	Gly	Val	Phe	Leu	Cys	Val	Ala	Met
1				5				10					15		

Phe	Ala	Cys	Gly	His	Ala	Arg	Ala	Asn	Met	Leu	Val	Tyr	Pro	Met	Ala
			20					25					30		

Ala	Glu	Ile	Asn	Ser	Ser	Arg	Glu	Glu	Ala	Thr	Ser	Leu	Phe	Val	Tyr
		35					40					45			

```
Ser Lys Ser Asp His Val Gln Tyr Ile Arg Thr Arg Ile Met Arg Ile
     50                  55                  60

Glu His Pro Gly Met Pro Gln Glu Lys Glu Val Pro Ala Gly Asn Asp
 65                  70                  75                  80

Ile Glu Thr Gly Leu Val Val Ser Pro Glu Lys Phe Ala Leu Ser Pro
                 85                  90                  95

Gly Thr Lys Lys Thr Ile Arg Val Ile Ser Thr Gln Ala Pro Glu Arg
            100                 105                 110

Glu Glu Ala Trp Arg Val Tyr Phe Glu Ala Val Pro Glu Leu Glu Asp
        115                 120                 125

Asp Pro Gln Ala Gly Gly Lys Gln Asn Ser Ser Val Ser Val Asn Leu
    130                 135                 140

Val Trp Gly Val Leu Leu Arg Val Ser Pro Ser Asp Pro Arg Pro Ala
145                 150                 155                 160

Leu Val Thr Asp Gly His His Leu Leu Asn Thr Gly Asn Thr Arg Leu
                165                 170                 175

Ser Leu Ile Arg Ala Gly Asn Cys Asp Thr Thr Cys His Trp Gln Asn
            180                 185                 190

Ile Gly Lys Ser Ile Tyr Pro Gly Gly Ser Ala Asp Ile Pro Ala Gly
        195                 200                 205

Ile Lys Ser Asn Ala Phe Arg Val Glu Tyr Arg Thr Gly Ala Asn Ser
    210                 215                 220

Pro Val Ile Ser Ala Asp Leu Thr Ala Ala Gly Lys
225                 230                 235
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<210> 3
<211> 191
<212> PRT
<213> Salmonella typhi

<400> 3

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Met Tyr Thr Glu Cys Thr Tyr Ile Thr Val Ile Asn Asn Lys Ala Arg
  1               5                  10                  15

Leu Phe Phe Met Asn Met Lys Thr Ser Phe Ile Ala Ala Ala Val Ala
             20                  25                  30

Leu Ala Thr Val Tyr Ser Phe Ser Val Ser Ala Val Gln Lys Asp Ile
         35                  40                  45

Thr Val Thr Ala Asn Ile Asp Ser Thr Leu Glu Leu Leu Gln Ala Asp
     50                  55                  60

Gly Ser Ser Leu Pro Ser Thr Met Lys Leu Asp Phe Met Pro Gly Lys
 65                  70                  75                  80

Gly Leu Val His Lys Ser Leu Gln Thr Arg Leu Tyr Ser Asn Asp Gln
                 85                  90                  95
```

```
Thr Lys Ser Val Asn Val Lys Leu Leu Asn Ala Pro Gln Leu Ile Asn
            100                 105                 110

Val Leu Asp Pro Thr Lys Thr Ile Asp Met Glu Val Thr Leu Gly Gly
        115                 120                 125

Arg Ser Leu Thr Thr Thr Asn Ser Val Leu Glu Ala Lys Thr Leu Phe
    130                 135                 140

Pro Asp Gly Lys Thr Gly Asp Ala Ser Ala Leu Leu Asn Leu Asp Ile
145                 150                 155                 160

Gly Gln Lys Ala Gly Ala Ala Leu Gln Asn Leu Pro Ala Gly Glu Tyr
                165                 170                 175

Ser Gly Leu Val Ser Leu Val Ile Ser Gln Ala Val Thr Ala Gly
            180                 185                 190
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<210> 4
<211> 889
<212> PRT
<213> Salmonella typhi

<400> 4

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Met Tyr Tyr Leu Leu Gly Leu Cys Ser Phe Thr Ser Gln Ala Thr Leu
  1               5                  10                  15

Ile Pro Pro Pro Gly Phe Glu Ser Leu Leu Glu Gly Gln Thr Glu Gln
            20                  25                  30

Ile Glu Val Leu Leu Pro Gly His Ser Leu Gly Leu Phe Pro Val Val
        35                  40                  45

Val Lys Pro Asp Thr Val Gln Phe Met Ser Pro Leu Met Val Leu Glu
    50                  55                  60

Ser Ser Gly Leu Ala Ala Leu Pro Ala Ala Glu Arg Gln Lys Ala Leu
65                  70                  75                  80

Ala Ala Leu Ser Arg Pro Leu Leu Arg Asn Ser Asn Leu Val Cys Gly
                85                  90                  95

Val Ser Glu Ala Lys Asp Ser Ser Glu Cys Gly Tyr Val Ala Thr Asp
            100                 105                 110

Lys Glu Asp Val Ala Val Ile Phe Asp Glu Asn Asn Ala Gln Leu Ser
        115                 120                 125

Leu Phe Leu Asn Arg Asp Trp Leu Pro Asp Glu Glu Arg Arg Asp Lys
    130                 135                 140

Arg Trp Leu Thr Pro Thr Pro Glu Gly Val Ser Ala Phe Ile His Arg
145                 150                 155                 160

Gln Thr Leu Tyr Leu Ser Asp Asp Leu His Ser Arg Asn Met Thr Leu
                165                 170                 175
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```
Asn Gly Ser Gly Ala Leu Gly Leu Gly Asp Gly Arg Tyr Leu Gly Gly
            180                 185                 190

Asp Trp Ala Ala Ile Trp Asn Gln Ser Glu His Tyr Asn Asn Ser Gln
        195                 200                 205

Ala Trp Phe Asp Asn Leu Phe Val Arg Gln Asp Leu Gly Asn Gln Tyr
    210                 215                 220

Tyr Leu Gln Ala Gly Arg Met Asp Gln Arg Asn Leu Ser Ser Ala Thr
225                 230                 235                 240

Gly Gly Asp Phe Gly Phe Ser Leu Leu Pro Leu Ser Arg Phe Asp Gly
                245                 250                 255

Leu Arg Thr Gly Thr Thr Gln Ala Tyr Val Asn His Glu Val Asp His
            260                 265                 270

Asn Ala Thr Pro Val Met Val Gln Val Thr Arg Asn Ala Arg Ile Asp
        275                 280                 285

Ile Tyr Arg Gly Ser Glu Leu Leu Gly Ser Gln Phe Leu Thr Pro Gly
    290                 295                 300

Met His Thr Leu Asp Thr His Ser Leu Pro Pro Gly Ser Tyr Pro Leu
305                 310                 315                 320

Ala Leu Arg Val Tyr Glu Asp Gly Ile Leu Arg Arg Thr Glu Thr Gln
                325                 330                 335

Pro Phe Ser Lys Gly Gly Asn Ser Phe Ser Ala Gln Thr Gln Trp Phe
            340                 345                 350

Ile Gln Gly Gly Leu Glu Asp Thr Gly Asp Lys Ala Ser His Tyr Asp
        355                 360                 365

Gly Glu Thr Val Met Ala Ala Gly Phe Gln Thr Gly Leu Arg Lys Asn
    370                 375                 380

Ile Ser Leu Thr Glu Gly Ile Ser Leu Ala His Glu Ala Trp Tyr Ser
385                 390                 395                 400

Glu Thr Arg Leu Asn Ser Gln His Ala Val Leu Asp Gly Thr Leu Asp
                405                 410                 415

Leu Ser Ala Gly Ile Leu His Gly Thr Asp Ser Thr Ser Gly Asn Thr
            420                 425                 430

Glu Gln Val Thr Tyr Asn Asp Gly Phe Ser Ala Ser Leu Trp Arg Asn
        435                 440                 445

His Thr Glu Ser Asp Ala Cys Ser Gly Arg His Pro Gln Ser Val His
    450                 455                 460

Ala Ser Met Thr Cys Gln Thr Ser Met Asn Ala Ser Leu Ser Val Ser
465                 470                 475                 480

Val Gly Asn Trp Tyr Ala Leu Leu Gly Tyr Ser Thr Ser Arg Thr Glu
                485                 490                 495
```

Gly Arg Pro Val Tyr Arg Gly Tyr Asp Asp Asn Ser Asp Lys Glu Asn
500 505 510

Val Phe Trp Arg Gln Ala Tyr Ile Pro Ala Ser His Arg Glu Ser Ala
515 520 525

Gln Ala Ser Ala Thr Tyr Ser Leu Asn Met Ala Gly Met Asn Ile Asn
530 535 540

Thr His Gly Gly Val Trp Arg Thr Arg Asn Asp Gly Val Asn Asp Asp
545 550 555 560

Gly Leu Phe Met Ser Val Ser Val Ser Tyr Ala Ser Gln Pro Pro Thr
565 570 575

Met Thr Gly Ser Asn Arg Tyr Thr Ser Ala Gly Thr Asp Ile His Ser
580 585 590

Ser Arg Asn Gln Lys Thr Gln Thr Ser Trp Asn Val Asn His Val Arg
595 600 605

Ser Trp Gln Gln Asp Leu Tyr Arg Glu Leu Ser Val Gly Phe Ser Gly
610 615 620

Tyr Asn Asp Asp Ser Trp Ser Gly Ser Leu Gly Gly Arg Met Ser Gly
625 630 635 640

Arg Met Gly Glu Leu Ser Ala Thr Ile Ser Asn Ser His Gln Arg Asn
645 650 655

Ala Gly Ser Ala Ser Ser Leu Thr Ala Gly Tyr Ser Ser Ser Leu Ala
660 665 670

Leu Ser Arg Asn Gly Leu Phe Trp Gly Gly Gly Gln Asp Gly Glu Pro
675 680 685

Ala Ser Gly Met Ala Val Asn Val Glu Ser Glu Gly Asp Glu Gly Ser
690 695 700

Ser Gly Lys Val Val Ser Val Arg Gly Ser Ser Gln Pro Phe Ser Leu
705 710 715 720

Gly Phe Gly Gln Gln Ser Leu Leu Leu Met Glu Gly Tyr Asn Ala Thr
725 730 735

Glu Val Thr Ile Glu Asp Ala Gly Val Ser Ser Gln Gly Met Ala Gly
740 745 750

Val Lys Ala Gly Gly Gly Ser Arg Cys Tyr Phe Leu Thr Pro Gly His
755 760 765

Leu Leu Val His Asn Ile Ser Ala Ser Met Ser Arg Leu Tyr Val Gly
770 775 780

Arg Val Leu Asp Lys Asp Gly Arg Pro Leu Leu Asp Ala Gln Pro Leu
785 790 795 800

Asn Tyr Pro Phe Leu Ser Leu Gly Pro Ser Gly Arg Phe Ser Leu Gln
805 810 815

```
Ser Glu His Lys Glu Ser Ser Leu Trp Leu Leu Ser Lys Asn Arg Ile
            820                 825                 830

Leu Arg Cys Pro Met Ser Val His Lys Arg Arg Asp Val Met Gln Val
        835                 840                 845

Val Gly Asp Val Arg Cys Glu Leu Ser Asp Val Asp Ala Leu Pro Gln
    850                 855                 860

Ala Leu Gln Ile Ser Pro Arg Val Ile Arg Leu Leu Asn Val Ala Gly
865                 870                 875                 880

Leu Leu Arg His Ser Val Gln Glu Ala
                885
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<210> 5
<211> 359
<212> PRT
<213> Salmonella typhi

<400> 5

```
Met Ser Asn Lys Met Lys Trp Thr Ser Met Thr Ala His Trp Ser Ala
  1               5                  10                  15

Ile Ile Asn Phe Ile Arg Lys Tyr Val Tyr Pro Ala Arg Ile Ile Ala
            20                  25                  30

Ile Leu Leu Met Ala Gly Ala Thr Leu Pro Gln Val Ala Asp Ala Ile
        35                  40                  45

Thr Val Asp Leu Asn Tyr Asp Lys Asn Asn Val Ala Val Ile Thr Pro
    50                  55                  60

Val Trp Ser Gln Glu Trp Ser Val Ala Asn Val Leu Gly Gly Trp Val
65                  70                  75                  80

Cys Arg Ser Asn Arg Asn Glu Asn Glu Gly Ala Cys Glu Glu Thr His
                85                  90                  95

Leu Val Trp Trp Tyr Ala Phe Gly Ala Tyr Ser Lys Ile Arg Leu Arg
            100                 105                 110

Phe Arg Glu Gln Ile Ser His Ala Glu Ile Thr Leu Ile Leu Leu Gly
        115                 120                 125

Ser Val Arg Asp Ala Cys Tyr Thr Gly Val Ile Asn Met Asn Ala Ala
    130                 135                 140

Ala Cys Gln Trp Gly Arg Ser Leu Lys Leu Arg Ile Pro Ser Glu Glu
145                 150                 155                 160

Leu Ala Lys Ile Pro Thr Ser Gly Thr Trp Lys Ala Thr Leu Val Leu
                165                 170                 175

Asp Tyr Leu Gln Trp Gly Gly Asp Asp Pro Leu Gly Thr Ser Thr Thr
            180                 185                 190

Asp Ile Thr Leu Asn Val Thr Asp His Phe Ala Glu Asn Ala Ala Ile
        195                 200                 205
```

```
Tyr Phe Pro Gln Phe Gly Thr Ala Thr Pro Arg Val Asp Leu Asn Leu
    210                 215                 220

His Arg Met Asn Ala Ser Gln Met Ser Gly Arg Ala Asn Leu Asp Met
225                 230                 235                 240

Cys Leu Tyr Asp Gly Gly Val Lys Ala Arg Ser Leu Gln Met Lys Ile
                245                 250                 255

Glu Gly Ser Asn Lys Ser Gly Thr Gly Phe Gln Val Ile Lys Ser Asp
            260                 265                 270

Ser Ala Asp Thr Ile Asp Tyr Ala Val Ser Met Asn Tyr Gly Gly Arg
        275                 280                 285

Ser Ile Pro Val Thr Arg Gly Val Glu Phe Ser Leu Asp Asn Val Asp
    290                 295                 300

Lys Ala Ala Thr Arg Pro Val Val Leu Pro Gly Gln Arg Gln Ala Val
305                 310                 315                 320

Arg Cys Val Pro Val Pro Leu Thr Leu Thr Thr Gln Pro Phe Asn Ile
                325                 330                 335

Arg Glu Lys Arg Ser Gly Glu Tyr Gln Gly Thr Leu Thr Val Thr Met
            340                 345                 350

Leu Met Gly Thr Gln Thr Pro
        355
```

<210> 6
<211> 151
<212> PRT
<213> Salmonella typhi

<400> 6

```
Met Thr Val Tyr Leu Asp Asp Lys Asp Lys Glu Leu Leu Lys Glu Ile
  1               5                  10                  15

Gln Lys Asp Cys Ala Gln Thr Leu Trp Gln Leu Ala Tyr Lys Val Gly
             20                  25                  30

Leu Thr Pro Thr Pro Cys Phe Lys Arg Leu Lys Lys Leu Lys Asp Arg
         35                  40                  45


Gly Val Ile Ile Gly Gln Phe Ala Leu Leu Asp Lys Glu Lys Leu Gly
     50                  55                  60

Leu Ser Leu Asn Val Phe Ile Met Ile Asn Ile Ser Glu Glu Gln Tyr
 65                  70                  75                  80

Ala Ser Ile Ser Glu Lys Ile Lys Ser Met Pro Glu Val Ile Ala Phe
                 85                  90                  95

Tyr Arg Ile Ser Gly Ser Phe Asn Tyr Leu Met His Thr Val Phe Thr
             100                 105                 110
```

```
Asp Met Asn Asp Tyr Tyr Ser Phe Tyr Glu Lys Ile Ile Leu Thr Asn
        115                 120                 125

Ser Ser Ile Ser Gly Ser Ala Ser Ser Phe Val Leu Glu Gln Ile Lys
    130                 135                 140

Glu Thr Asn Glu Leu Ser Val
145                 150
```